DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Docket No. FDA-2010-N-0621

Proposal to Withdraw Approval for the Breast Cancer Indication for AVASTIN (Bevacizumab)

DECISION OF THE COMMISSIONER

November 18, 2011

COMMISSIONER'S DECISION

Avastin (bevacizumab) is a drug that has been approved by the Food and Drug Administration (FDA) for the treatment of several types of cancer. On February 22, 2008, FDA's Center for Drug Evaluation and Research (CDER) approved Avastin for use in combination with paclitaxel in the treatment of patients who have not received chemotherapy for metastatic HER2-negative breast cancer. This approval was under the rules for accelerated approval set forth in FDA regulations (21 C.F.R. § 601.40-46) and the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 506). Accelerated approval may be granted to drugs to treat life-threatening conditions for which there is unmet medical need in circumstances in which there are not sufficient data to justify a regular approval of a drug, but the evidence that is available provides a reason to hope that, once more testing has been completed, a the drug's safety and effectiveness will be confirmed. Accelerated approval is granted upon the condition that the drug's sponsor must diligently conduct additional studies to confirm and describe its benefit. Drugs that have been granted accelerated approval are subject to accelerated withdrawal of approval if the studies fail to verify clinical benefit or if the drug is not shown to be safe and effective.

CDER's decision to grant accelerated approval for Avastin's use in the treatment of breast cancer was not based on a showing that the drug helped patients live longer or improved their quality of life during the time during which they battled their cancer. There was not, at the time of approval, credible evidence of increased overall survival or increased quality of life, and there is no such evidence now. Instead, CDER based its accelerated approval on a different measure,

referred to as "progression free survival" (PFS). PFS measures the interval between the time a patient is assigned to the control or investigational arm of a drug trial and either death or evidence, generally from radiological assessments, that the size of the tumor has increased. For a drug like Avastin, which has serious side effects, a small increase in PFS without a showing of improved survival or improvement in quality of life does not provide a clinical benefit that is meaningful to patients.[1] But at the time of the accelerated approval decision, there was evidence of a 5.5 month increase in median PFS, which was both statistically significant and of sufficient magnitude, based on one clinical trial. That increase was the basis for the approval.

On November 16, 2009, Avastin's sponsor, Genentech, Inc. submitted data from the trials that Genentech and FDA had agreed upon to confirm the benefit of the drug for this indication. The studies did not confirm that the increase in PFS was as substantial as the original study had suggested. On review, CDER concluded that these studies did not verify clinical benefit, and that the available evidence indicated that the drug was not shown to be safe and effective. It therefore proposed to withdraw the breast cancer indication, and, pursuant to FDA regulations (21 C.F.R. 601.43), in December 2010 CDER published a notice of opportunity for hearing to allow Genentech to respond.

Genentech requested a hearing, arguing that this approval should not be withdrawn.[2] Pursuant to the regulations, and as described more fully below, a hearing was held and CDER, Genentech, and the public were provided an opportunity to comment on CDER's proposal. On the basis of the administrative record of this hearing and the comments submitted to the public

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[1] Guidance for Industry, *Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics*, 8 (May 2007), available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590.pdf.

[2] As discussed in more detail below, as the hearing process has gone forward, Genentech has placed increasing weight on the idea that the approval could be modified somewhat, and that it could be allowed to continue to sell this drug as approved by FDA for the treatment of metastatic breast cancer under certain conditions: an indication that it believes is narrower and would reflect the more recent data; additional cautions given to patients and prescribers; and marketing that would be limited and overseen by FDA.

docket, I conclude that the continued labeling of Avastin for the treatment of metastatic breast cancer is not justified and that the approval should be withdrawn.

The reasons for my decision are explained in detail in the remainder of this document. In section I of this document, I will speak directly to the concerns raised by patients and those who support them regarding the decision and its implications for them. I will then, in section II, provide background on Avastin and on metastatic breast cancer, and on the pivotal issue of what constitutes clinical benefit for this drug for this use. In section III of this decision, I will describe the legal standard that applies to decisions whether to withdraw approval under the accelerated approval authority applicable here.

I will then describe, in section IV, the process by which Avastin was approved for the metastatic breast cancer indication, the developments that led to the proposal to withdraw its approval, and the administrative hearing that we held on these issues. In section V, I will explain my reasons for concluding that, when the appropriate legal standards are applied to the facts presented here, withdrawal of approval is the appropriate action. In this section I will also address various arguments that Genentech has made in support of its request for a continued accelerated approval of its product for this use.

I. AN EXPLANATION FOR PATIENTS AND THOSE WHO SUPPORT THEM

This document, which lays out the basis for my decision, has several purposes. It is an explanation, for physicians, scientists, patients and the public in general, of the data available on the metastatic breast cancer indication for Avastin and of FDA's evaluation of those data. It also describes how FDA has applied the law and its regulations in making the decision to withdraw the approval for that indication.

I know I speak on behalf of the many physicians that have been involved with this issue here at the Food and Drug Administration and elsewhere in saying that we encourage patients, and those who support them, to ask hard questions and to demand explanations concerning the drugs that are recommended to treat serious illnesses. I will address here some of the questions that patients and their supporters may have about this decision.

Does the FDA decision mean that patients will not be able to use Avastin for the treatment of breast cancer? The short answer to this question is "No." FDA does not regulate the practice of medicine, and it is part of the practice of medicine for a physician to be able to prescribe a drug that is approved for one use (and Avastin continues to be approved for use in several cancers) for another, unapproved use. Thus, a physician can prescribe Avastin for the treatment of breast cancer if he or she chooses to do so, despite the withdrawal of approval of that use.

Does the FDA decision mean that patients will lose insurance coverage for the use of Avastin for the treatment of breast cancer? This is a more complicated question. FDA's decisions have no direct effect on insurance coverage. At this point, the Centers for Medicare and Medicaid Services (CMS) has said that it is continuing to reimburse for this use. While health insurance contracts with private providers obviously vary, it is our understanding that private insurers do cover the use of drugs for unapproved uses in those circumstances in which that use is considered appropriate medical practice. They may continue to reimburse for the use of Avastin for the breast cancer indication (use with paclitaxel), as many apparently now reimburse for use of Avastin with anti-cancer drugs other than paclitaxel even though use in combination with other drugs has never been approved by FDA. To be very clear, FDA's decisions on approval do not require any change in insurance coverage.

If I, as a patient, and my treating physician believe that Avastin is the right drug to treat my breast cancer, why shouldn't FDA approve the drug for that use? By law, FDA can only approve a drug for a particular use if there is credible, objective evidence that the drug is safe and effective for that use. This is, in effect, what FDA approval means; that the public and physicians can have confidence that claims made about a drug in its labeling have been carefully and impartially reviewed, and that they are supported by evidence. This requirement provides an essential protection to the public. When Congress first required FDA to begin evaluating the effectiveness of drugs in 1962, it required sponsors of drugs that had been on the market without proof of their effectiveness through adequate and well-controlled clinical trials to perform those trials and submit the evidence to FDA. Ultimately FDA found that many drugs that had been in common use prior to 1962, and that both doctors and patients had believed to be effective, were not shown by objective testing to be effective for the uses for which they were labeled.

There are many reasons why patients and physicians believe in drugs, whether based on personal experience or on their own evaluation of evidence. Over the years FDA's decisions with respect to particular drugs have often been questioned by those who preferred to rely on their own beliefs. In some cases, the disputes involved differing evaluations of carefully done clinical trials. In others, there was little or no scientific data to support those strongly held beliefs.

Ultimately, my responsibility, and the agency's responsibility, is to put aside any preconceived beliefs that I, or patients or physicians may hold, and take a hard look at the objective evidence. We may hope, as CDER scientists did when they granted the initial accelerated approval of Avastin for the breast cancer indication, that the additional studies

conducted to support continued approval of a drug that has shown promise in an initial trial will confirm the effectiveness of the drug. But if the evidence does not show that, FDA cannot, and should not, continue to approve it.

Since FDA had already announced its decision to withdraw approval of Avastin for the breast cancer indication, did Avastin receive a fair hearing? As explained elsewhere in this decision, FDA has taken advantage of the way our agency is structured to assure that the hearing was fair. Within our agency, CDER is generally responsible for decisions with respect to the approval of this type of drug. That Center granted the accelerated approval of Avastin for the breast cancer indication in the first place, and then, based on new data, it made the determination that that approval needed to be withdrawn. I, as Commissioner, am not normally involved in drug approval decisions, and I was not involved in either the decision to approve this indication or CDER's initial decision to withdraw approval. When Genentech objected to the CDER decision to withdraw approval, it exercised its right to seek a hearing on that decision.

In conducting the hearing, FDA decided to utilize something called the "separation of functions" to protect the independence of the Commissioner's decision and make the process transparent. Under separation of functions, I as Commissioner (and those assisting me on this issue, such as Dr. Midthun, the Director of FDA's Center for Biologics Evaluation and Research who served as presiding officer at the hearing) communicated with CDER about the subject of this hearing only as part of the formal hearing record, in exactly the same way that we communicated with Genentech. CDER presented its views as a party in the hearing, as did Genentech. As the applicant, Genentech was a motivated, knowledgeable, and well represented proponent of its view. Both CDER and Genentech presented evidence at the hearing and challenged each others' presentations. In addition, members of the public submitted comments to

the docket and testified at the hearing. That created the record that led to my own decision as Commissioner. I did not know, until review of that record and discussion of the issues with Dr. Midthun, how I would decide the issues presented. I have now made that decision based on the evidence.

How can FDA make a different decision than was made by the regulatory authorities in Europe? It is true that the European Medicines Agency has continued to approve Avastin for use with paclitaxel in the treatment of metastatic breast cancer, though the United Kingdom's National Institute for Health and Clinical Excellence (NICE) has not recommended Avastin's use with taxanes as a first-line treatment for people with metastatic breast cancer.[3] The regulatory standards for different government agencies may vary somewhat, and of course the decision-makers are different in different places. I can only apply the United States standards to the evidence that has been provided to FDA. That is what I have done in this decision.

Is it possible that Avastin might be approved, once again, for the treatment of certain patients suffering from metastatic breast cancer? Genentech has said that it will consider conducting a further adequate and well-controlled clinical trial that would be designed to show that the use of Avastin with paclitaxel would be safe and effective for patients, or for some subset of patients. If such a trial were completed and showed a clear benefit for this use, such as increased overall survival, better quality of life, or even a substantial increase in "progression free survival" of the type seen with the E2100 study that formed the basis for the initial accelerated approval, a new approval could be granted. In addition, Genentech has said that it would consider including in such a trial a mechanism to determine whether certain patients (those with high plasma levels of Vascular Endothelial Growth Factor-A (VEGF-A)) would

[3] http://www.nice.org.uk/newsroom/pressreleases/AvastinBevacizumabNotRecommended.jsp; http://guidance.nice.org.uk/TA214.

benefit most from use of Avastin. If such a therapeutic relationship could be demonstrated, that might represent a basis for Avastin to be approved for use by certain patients.

Ultimately, if Genentech does go forward with the new clinical trial that it has discussed, that will lead to more scientific evidence on the question of whether or not Avastin might provide a benefit for some patients in the treatment of metastatic breast cancer. At this stage, however, based on the evidence currently available, I have concluded that continued accelerated approval of Avastin for this use is not justified.

II. BACKGROUND

A. Avastin

Avastin (bevacizumab) is a recombinant, humanized monoclonal (IgG1) antibody that binds to and inhibits the biological activity of human vascular endothelial growth factor ("VEGF"), a protein that is important for the formation of blood vessels. Avastin has been tested in clinical trials in multiple tumor types, and it is thought that the drug may work by preventing the formation of new blood vessels that would otherwise maintain a tumor or allow it to grow.[4]

Avastin was approved by CDER on February 26, 2004 as a first-line treatment in combination with intravenous 5-fluororacil-based chemotherapy in patients with metastatic carcinoma of the colon and rectum. Since then, Avastin has been approved for non-squamous non-small-cell lung cancer in combination with carboplatin and paclitaxel for first-line treatment of unresectable, locally advanced, recurrent or metastatic disease; glioblastoma, as a single agent for adult patients with progressive disease following prior therapy (accelerated approval); and metastatic renal cell carcinoma with interferon alfa. Joint Statement ¶ 2. None of these

[4] *See* "Joint Statement of Undisputed Facts and Select Issues in Dispute (Joint Statement), Docket No. FDA-2010-N-0621-0132.¶ 1,. *See also* FDA Briefing Document, ODAC Meeting of July 20, 2010, 5. This briefing document, and other documents pertaining to the 2010 ODAC meeting cited in this decision, are available in Docket No. FDA-2010-N-0621-0145, Appendix 18 unless otherwise noted.

indications has been at issue in this proceeding, and CDER has not proposed to withdraw or modify any of them. Joint Statement ¶ 3.

B. Metastatic breast cancer

Metastatic breast cancer is, at present, an incurable disease. According to the American Cancer Society, it is estimated that more than 40,000 women in the United States died from metastatic breast cancer in 2009, and that over 90% of patients diagnosed with metastatic breast cancer ultimately die from the disease. Joint Statement ¶ 5. The main goals of therapy are palliation of symptoms and prolongation of overall survival time without negatively impacting quality of life. Metastatic breast cancer is also a heterogeneous disease, for which no single therapeutic approach is appropriate for all patients. The appropriate treatment strategy for a particular patient depends on multiple individualized factors, including tumor burden and related symptoms, underlying tumor biology, age and medical co-morbidities, and prior treatment. Joint Statement ¶ 6.

Approximately 70-75% of primary breast cancers are HER2-negative. HER2 is an acronym for "human epidermal growth factor receptor 2," a protein that promotes tumor growth. Patients whose tumors over-express the HER2 protein or have more than two copies of the HER2 gene (gene-amplified) are considered to have HER2-positive metastatic breast cancer. Patients whose tumors do not over-express the HER2 protein or are not gene-amplified are considered to have HER2-negative metastatic breast cancer. Joint Statement ¶ 7.

Treatment options for patients with metastatic breast cancer include the use of single-agent or combination chemotherapy, hormonal therapy, and biological therapy. Joint Statement

¶ 8[5]. Nevertheless, these therapies provide limited benefit, and there is unmet medical need for additional safe and effective therapies for metastatic breast cancer. Joint Statement ¶ 4.[6]

C. Effectiveness for cancer treatments

In the context of oncology drugs, and particularly for diseases that are not curable like metastatic breast cancer, clinical benefit usually means a therapy that can prolong life or improve the quality of life by easing the burden of symptoms or restoring function. Above all, a demonstration that a therapy can prolong life has long been, and remains, the gold standard for approval. CDER has for that reason urged sponsors to design their trials to determine whether a candidate drug improves overall survival.[7]

Nevertheless, CDER has concluded, and I agree, that an improvement in PFS may constitute clinical benefit in appropriate circumstances.[8] CDER developed its policy on this

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[5] Other FDA-approved agents include: methotrexate, cyclophosphamide, thiotepa, vinblastine, 5-fluorouracil, and doxorubicin for metastatic breast cancer; paclitaxel, docetaxel, trastuzumab, capecitabine, capecitabine plus docetaxel, abraxane, lapatinib, and ixabepilone for 2nd and 3rd-line treatment; trastuzumab plus paclitaxel and gemcitabine plus paclitaxel for 1st line treatment. FDA Briefing Document for 2010 ODAC Meeting 5-6.

[6] Genentech points to a statement made by a CDER official during the hearing to suggest that CDER may not believe there is unmet need for first-line therapy for patients with metastatic breast cancer. Post-Hearing Submission of Genentech, Inc. In Support of Maintaining the Accelerated Approval of AVASTIN® (Bevacizumab) in Combination With Paclitaxel for the First-Line Treatment of HER2-Negative Metastatic Breast Cancer (Genentech Post-Hearing Submission), Docket No. FDA-2010-N-0621-0478, 13-14. However, CDER's position is that there is unmet need, as reflected in the parties' joint statement. *See also* Letter from Dr. Janet Woodcock to Breast Cancer Community, Dec. 16, 2010, available at http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM237286.pdf ("[T]here are not enough effective treatments for this cancer."). The question of whether there is unmet need for additional safe and effective treatments for this cancer is not in dispute, and my decision is premised on the understanding that there is unmet need in this area.

7 Transcript of Public Hearing on Proposal to Withdraw Approval for the Breast Cancer Indication for Bevacizumab (Avastin), June 28, (hereafter, June 28 Tr.), 283:15-284:16; FDA Briefing Document for 2010 ODAC Meeting 5. The clinical endpoint by which survival is generally measured is referred to as "overall survival" (OS). It is defined as the time from randomization until death from any cause, and is measured in the intent-to-treat population. *Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics* (May 2007), 5.

[8] As Genentech points out, and as CDER also recognizes, it can be difficult to design a trial to measure OS for an oncology drug intended for first-line treatment. Patients may switch therapies during a trial if they find they cannot tolerate the investigational drug, and may even begin taking the control drug; many will take second- and third-line therapies after a trial concludes. These changes in therapy make it difficult to isolate the effect of the investigational drug. Mature OS data may also take years to develop. For these and other reasons, CDER, and the oncology community generally, have considered whether time to tumor progression, or other tumor-based effects that can be measured relatively quickly and more easily attributed to the first-line therapy, are appropriate to use as an alternative measure of clinical benefit.

matter over several years, after receiving input from the public, industry, and medical experts, ultimately concluding that PFS may serve as a basis for drug approval, with the important caveat that "[w]hether an improvement in PFS represents a direct clinical benefit ... depends on the magnitude of the effect and the risk-benefit of the new treatment compared to available therapies." Guidance for Industry, *Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics*, 8 (May 2007), available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590.pdf. The limitation is essential because, as noted, PFS does not directly measure whether a treatment prolongs life or improves the quality of life. Small increases in PFS, even if they are demonstrated to be statistically significant by adequate studies, must be weighed against the drug's risk and may not represent meaningful benefit to patients. CDER has also approached PFS with care because measuring PFS raises substantial methodological problems. For example, tumor progression is typically measured at office visits, and cannot be recorded as precisely as survival time; radiographic measurement is technically difficult and requires the exercise of judgment; and many patients may be lost to a study before final PFS measurements are taken.[9]

The consideration of risks associated with a drug is a very significant issue with respect to Avastin and its use with respect to metastatic breast cancer. We know, from the clinical trials of Avastin, as well as our experience with this drug in the context of treatment of other cancers,

[9] CDER has long recognized these and other concerns with measurements that turn, in part, on tumor-based endpoints, *see, e.g.*, 2007 ODAC Meeting Tr. 14:4-17:10, available in FDA-2010-N-0621-0145, Appendix 10, and has sought input from experts and the public. In 1999, ODAC recommended that a related measure of tumor growth, time to progression (TTP), should not be considered clinical benefit in the context of first-line treatment of metastatic breast cancer, and since then, CDER has not used TTP as the basis of approval for a first-line agent for treatment of metastatic breast cancer. More recently, after further consideration of its general PFS policy and the specific context of treatments for first-line breast cancer such as Avastin, CDER concluded that PFS could constitute clinical benefit for a new first-line treatment, provided that there is also follow-up study to ensure that the drug did not undermine survival. Genentech has recognized that CDER's openness to the possibility that PFS benefit of a sufficient magnitude may constitute clinical benefit represents "progressive thinking" on the part of the agency. Transcript of Public Hearing on Proposal to Withdraw Approval for the Breast Cancer Indication for Bevacizumab (Avastin), June 29, 2011, (hereafter, June 29 Tr.), 7:15-21.

that it presents significant risks to patients. It may even cause death. This is a particularly important issue in light of the fact that patients may be diagnosed with metastatic breast cancer when they are still symptom-free, as were many patients in the E2100 trial. Exposure of such patients to significant adverse events, or even death, at a time when the patient, though facing an incurable and likely terminal disease, is otherwise capable of performing and enjoying life's functions can be justified only if the possibility that the patient will benefit is real.

This leads us to the essential question that FDA faces whenever it is asked to determine whether a drug has been shown to be safe and effective: does it offer a benefit that is meaningful to a patient in light of its risks, disease stage, and alternative therapies? No one would argue, for example, that a drug that had been shown to be effective in treating a common headache could be considered safe and effective if it frequently caused serious side effects in the patients using it. On the other hand, a drug that provides substantial benefit in the treatment of patients with otherwise incurable cancer might be found to be safe and effective even though it carries serious risks. Thus, FDA has found that Avastin is safe and effective for the treatment of several types of cancer despite the fact that the evidence shows that it may also subject patients to significant side effects, including, for some patients, death.

One question that has arisen during the hearings is whether there is a threshold improvement in median PFS that would have to be shown in the studies to establish a clinical benefit for Avastin for the treatment of metastatic breast cancer. There is not a simple answer to this question, because median PFS improvement, which has so far figured prominently in discussions of Avastin, is only one of several factors that must be considered. In addition, one must consider the PFS effect in terms of the hazard ratio; other evidence, if any, with respect to other measures of efficacy, such as overall survival and/or improvement in quality of life; the

risks associated with use of the drug; and the level of confidence that the clinical study data accurately represent what will happen to patients in clinical use of the drug. The totality of the evidence must be considered in evaluating clinical benefit.

As discussed in detail in other parts of this decision, one of the first studies that Genentech submitted for Avastin's breast-cancer indication, E2100, showed a PFS increase that CDER said would constitute clinical benefit if it could be confirmed in subsequent studies; this included an increase in median PFS of 5.5 months with hazard ratio of 0.48, no evidence of an effect on overall survival or improved symptoms, and a safety profile that included serious risks, but not risks that were unanticipated in light of previous experience with the drug. A threshold level has not been set that formally defines what lesser showing of PFS improvement, if any, would be sufficient for approval, and particularly what showing of improvement in median PFS would be necessary.

I understand why companies seeking to develop drugs, and advocates for this use of Avastin, would prefer to have more certainty about the threshold for approval. I, and the agency, are committed to working with the developers of new drugs to design useful trials that can definitively answer questions about drug approval. At this point, however, in light of the agency's limited experience in using PFS as a measure of effectiveness for first-line metastatic breast cancer therapies and the evidence that is available, and because of the multiple factors that an approval decision would require the agency to consider, it would not be appropriate to announce a bright-line cut off of median PFS improvement that would be necessary to establish safety and effectiveness.[10] Instead, I must focus on the particular circumstances presented here and determine whether the full body of available data justifies a conclusion that the use of

[10] As discussed below, the multiple factors that must be considered with respect to each drug also make comparisons of FDA's approval decisions with respect to different drugs inappropriate in the context of the type of hearing involved here.

Avastin for the treatment of metastatic breast cancer has been shown to be safe and effective. The bases for my conclusions on that point are discussed in further detail below.

III. LEGAL STANDARD

In 1992, FDA issued regulations that provide a pathway for accelerated approval of new drugs and biologicals that are intended to treat serious and life-threatening illnesses for which there are limited treatment options, contingent on further study of the drugs' clinical effects after approval to confirm effectiveness. 21 C.F.R. § 601.40, Subpart E (§§ 601.40-46).[11] In 1997, Congress enacted section 506 of the FD&C Act, which essentially codifies in the statute FDA's accelerated approval regulations.[12]

The accelerated approval pathway represents a balanced approach. It recognizes, first, that patients with serious and life-threatening illnesses for which there are limited or no treatment options (i.e., unmet medical need) have an especially urgent need for the rapid development of new therapies, and that it may take many years to complete clinical trials that are able to provide substantial evidence of the kind of clinical benefit required for regular approval pursuant to FD&C Act section 505(d). The regulations therefore provide that new drugs being developed to treat such patients may be approved on the basis of different types of data, subject to a requirement to conduct confirmatory studies that will verify and describe their clinical benefit.

Specifically, accelerated approval may be based on (1) "an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit"; or, (2), as in the case of Avastin, "an effect on a clinical endpoint other than survival or irreversible morbidity." 21 C.F.R. § 601.41; *see also* FD&C Act

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[11] Proposed Rule, New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval, 57 Fed. Reg. 13234 (April 15, 1992); Final Rule, 57 Fed. Reg. 58942 (December 11, 1992).

[12] This is reflected both in the text of section 506 and in the legislative history. *See, e.g.*, House of Representatives Report 105-310, 55 ("New FDCA subsection 741(b) [current section 506(b)] provides an alternative basis for approving fast track products that essentially codifies FDA's accelerated approval regulations.")

§ 506(a)(1), (b)(1). Such approvals are still contingent on a risk-benefit determination by the agency that in light of the expected clinical benefit and risk profile of the drug, approval is appropriate. Such approvals are also conditioned on a drug sponsor's agreement to conduct studies to verify and describe clinical benefit, 21 C.F.R. § 601.41; FD&C Act § 506(b)(2), and mechanisms for expedited withdrawal of approval are provided, 21 C.F.R. § 601.43, FD&C Act § 506(b)(3). Confirmatory studies and expedited withdrawal of approval are an essential element of the accelerated approval process, because in some cases the promise shown by early research will not be borne out. The agency must be able "to withdraw approval rapidly in the event it loses the assurances regarding demonstration of actual clinical benefit. ... Otherwise, the risk of continued exposure of patients with serious or life-threatening diseases to ineffective or unsafe drugs outweighs the potential benefits." 57 Fed. Reg. at 13239.[13]

Section 506(b)(3) of the FD&C Act sets out four bases for expedited withdrawal of approval of a product approved under the accelerated procedures. Section 601.43(a) sets out six bases. With respect to Avastin, there appears to be agreement that two of the bases are at issue, and these two bases appear in both the regulations and the statute.

The first of these, which is set out in nearly identical language in § 601.43(a)(1) and section 506(b)(3)(B) of the FD&C Act, is that FDA may withdraw approval if, in the words of the regulation: "A postmarketing clinical study fails to verify clinical benefit", or, in the words of the statute, if: "[A] post-approval study of the fast track product fails to verify clinical benefit of the product."

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[13] *See also* 57 Fed. Reg. at 58954 ("Should well-designed postapproval studies fail to demonstrate the expected clinical benefit, the benefit expected at the time of approval (reasonably likely to exist) would no longer be expected and the totality of the data, showing no clinical benefit, would no longer support approval."); 57 Fed. Reg. at 13238 (If clinical benefit is not demonstrated in confirmatory studies, "the risk-benefit analysis changes significantly..." and continued marketing of the drug "is inappropriate and marketing approval should be rapidly withdrawn....")

In this case, the parties agree that "During CDER's review of [the sBLA], Genentech proposed and CDER agreed that the AVADO and RIBBON1 trials could serve as the required trial(s) to verify and describe the clinical benefit." Joint Statement ¶ 31. Thus, under the regulations (and the statute) FDA may withdraw the application if the AVADO and RIBBON1 trials fail to verify the clinical benefit of Avastin for the breast cancer indication for which it was approved.

CDER also argues that it would be appropriate to withdraw the metastatic breast cancer indication on a second, alternative, ground. This ground is also set forth in the regulation and in the statute. Section 601.43(a)(6) states that FDA may withdraw approval if: "Other evidence demonstrates that the biological product is not shown to be safe or effective under its conditions of use." Section 506(b)(3)(C) of the FD&C Act states that withdrawal is authorized if: "[O]ther evidence demonstrates that the fast track product is not safe or effective under the conditions of use."

In this case, the parties have agreed that the FDA-approved prescribing information for Avastin "is a fair and accurate description of the safety profile of Avastin," and that "[t]he safety data observed in the E2100, AVADO, and RIBBON1 studies were consistent with the safety profile of Avastin described in its approved prescribing information." Joint Statement, ¶¶ 22, 23. In light of this agreement, the dispute with respect to this issue centers on the effectiveness information for the breast cancer indication, and on the appropriate risk-benefit analysis to be made in light of that information as compared to the agreed risk of the product.

As noted, the safety profile of Avastin described in its approved prescribing information includes a black box warning concerning gastrointestinal perforation, surgery and wound healing complications, and severe or fatal hemorrhage. Genentech agrees that this warning is

appropriate, and it does not state that the use of this drug in the treatment of breast cancer is safe in the abstract. Instead, it states that the drug should be found to be safe because its use provides benefits to patients that outweigh its risks. Applying the standard in the regulation and statute to the facts presented, therefore, FDA may withdraw the indication if: (a) the available evidence on Avastin demonstrates that the drug has not been shown to be effective for the breast cancer indication for which it was approved, or (b) if the available evidence on Avastin demonstrates that the drug has not been shown to be safe for the breast cancer indication for which it was approved, in that Avastin has not been shown to present a clinical benefit that justifies the risks associated with use of the product for this indication.

A third issue is presented by the fact that both section 506(b)(3) of the FD&C Act and section 601.43(a) do not by their terms require the withdrawal of an accelerated approval even if the bases for withdrawal they describe are present. Instead, in each case, the statute and regulation state that FDA "may" withdraw approval in those circumstances. This standard reflects the fact that decisions on withdrawals of approval of products necessarily reflect judgment on FDA's part as to what actions are appropriate to protect the public with respect to approved products, and what uses of those products should be stated on the labels of those products.[14] Accordingly, if either of the two grounds for withdrawal set out above are found, I must decide a third issue, which is whether FDA should nevertheless continue the approval of

[14] As FDA has stated elsewhere, "Failure to confirm clinical benefit in a completed trial ... may reflect, for example, unforeseen limitations in trial design, rather than clear evidence of lack of effectiveness," and when trials "do not appear to confirm clinical benefit, FDA must carefully assess each case, and consider the underlying reasons and the consequences of all regulatory options, including their potential impact on patients." U.S. Government Accountability Office, New Drug Approval: FDA Needs to Enhance Its Oversight of Drugs on the Basis of Surrogate Endpoints, GAO-09-866 (Sept. 2009), App. V, FDA Comments on GAO Report at 3.

the breast cancer indication while Genentech designs and conducts additional studies intended to verify clinical benefit.[15]

IV. PROCEDURAL HISTORY

A. Genentech's supplemental submission for the metastatic breast cancer indication

In a supplemental Biologics License Application (sBLA)[16] dated May 23, 2006 (sBLA 125085/91), Genentech requested that FDA approve Avastin, in combination with taxane-based chemotherapy,[17] for the treatment of patients who have not received chemotherapy (first-line) for their locally recurrent or metastatic breast cancer. Joint Statement ¶ 26. With this supplement, Genentech submitted data and analysis for two clinical studies, E2100 and AVF2119g.

The E2100 study was a randomized, open-label trial in the first-line treatment of metastatic breast cancer. This was a multicenter Phase III study led by the National Cancer Institute Therapy Evaluation Program and coordinated by the Eastern Cooperative Oncology Group ("ECOG"). Joint Statement ¶ 9. The study investigated the combination of paclitaxel and Avastin compared to paclitaxel alone. The study enrolled 722 patients, predominantly in the United States. Joint Statement ¶ 10. The primary endpoint studied in the E2100 study was PFS, which was defined as the length of time from the date on which a patient is randomized to a control or treatment arm of a clinical trial until disease progression or death occurs, whichever comes first. Joint Statement ¶ 11. In E2100, disease progression was considered to be tumor

[15] I have described the issues for decision as Dr. Midthun did when she wrote the parties on May 6, 2011 regarding the nature and conduct of these proceedings, which is also the way that the issues were presented in the Federal Register notice for the hearing. The proceedings before the hearing, the hearing itself, and the parties' post-hearing submissions have all gone forward on this basis. Neither CDER nor Genentech has indicated that it disagrees with this description of the issues. I do note that although Genentech does not challenge the safety information on Avastin's metastatic breast cancer labeling, it has presented arguments and information that bear on how that information should be understood. I have taken that into account in this discussion of the issues, and will also discuss Genentech's presentation with respect to this issue below.

[16] As noted, Avastin is approved for several different cancer indications. Because it is a biologic product, that approval has occurred through a biologics license application (BLA) submitted pursuant to section 351 of the Public Health Service Act. After the first approval, additional approvals may be sought, as here, through the submission of supplemental BLAs.

[17] "Taxanes" are a class of chemotherapies that includes paclitaxel and docetaxel.

growth, which was measured primarily by radiographic measurement. Secondary efficacy endpoints that were included in the trial were overall survival (OS) (which is the time from randomization until death from any cause) and objective response rate (ORR) (objective response is a complete or partial response to treatment determined by two consecutive investigators' assessments which are four or more weeks apart; objective response rate is the percentage of patients who have objective responses). Joint Statement ¶ 12. The parties agree that the following table accurately summarizes efficacy data from the E2100 study[18]:

Study Arm	**Median PFS** (months)	**Median OS*** (months)	**ORR**
E2100			
Paclitaxel + Avastin	11.3	26.5	48.9%
Paclitaxel	5.8	24.8	22.2%
Between-Arm Difference	5.5	1.7	26.7%
Hazard Ratio (95% CI)	0.48 (0.39, 0.61)	0.87 (0.72, 1.05)	(18.4%, 35%)
	$p < 0.0001$	$p = 0.137$	$p < 0.0001$

* Updated OS analysis where available. CI = confidence interval; NR = not reached.

[18] Joint Statement, ¶ 13, Attachment 2. "OS", as noted above, refers to overall survival, which is the time from randomization until death from any cause, and is measured in the intent-to-treat population. Note that the hazard ratio is reported with a 95% confidence interval. That means that in 95% of situations the true hazard ratio will fall between the two numbers in parentheses. The p value is a measure of statistical significance. Generally, a p value below .05 is considered to be significant and a value above that is considered not to be significant. Thus, in this chart, there is considerable confidence that the hazard ratio for PFS favors the Avastin-paclitaxel combination and that the difference in median length of PFS is statistically significant in the study. On the other hand, there is no compelling evidence of a favorable hazard ratio relating to overall survival or increase in median length of overall survival.

A survey instrument administered to patients did not demonstrate an improvement in quality of life.[19] As noted, Genentech and CDER agree that the prescribing information for Avastin represents a fair and accurate summary of the safety data in E2100.[20] The labeling notes that

[19] The survey instrument was the Functional Assessment of Cancer Therapy (FACT-B), which has scales for patient social/family well-being, emotional well-being, physical well-being, functional well-being, and a subscale specific to breast cancer. CDER and Genentech agree that the instrument did not demonstrate clinical benefit with Avastin. *See, e.g.*, FDA Briefing Document, 2007 ODAC meeting, 5; 2007 ODAC meeting Tr. 213:22-213:4 (statement by Genentech expert) (Dr. Winer: "[T]hat is why we're having this discussion about progression-free survival because we simply don't have the kind of quality of life data here that we can rely upon.") Unless otherwise noted, documents pertaining to the 2007 ODAC meeting cited in this decision are available in Docket No. FDA-2010-N-0621-0145, Appendix 10.

[20] Joint Statement ¶ 22. *See also id.* Attachment 1 (copy of Avastin prescribing information, as of the date of the June hearing, hereafter "Avastin Prescribing Information"). As reflected in the prescribing information, Avastin has serious toxicities, and is associated with serious and life-threatening adverse events. The prescribing information includes a boxed warning (commonly referred to as a "black-box warning") because of a risk of gastrointestinal perforation, surgery and wound-healing complications, and severe or fatal hemorrhage. Avastin Prescribing Information, 3. The boxed warning reads:

> **WARNING: GASTROINTESTINAL PERFORATIONS, SURGERY AND WOUND HEALING COMPLICATIONS, and HEMORRHAGE**
> Gastrointestinal Perforations
> The incidence of gastrointestinal perforation, some fatal, in Avastin-treated patients ranges from 0.3 to 2.4%. Discontinue Avastin in patients with gastrointestinal perforation. [See Dosage and Administration (2.4), Warnings and Precautions (5.1).]
> Surgery and Wound Healing Complications
> The incidence of wound healing and surgical complications, including serious and fatal complications, is increased in Avastin-treated patients. Discontinue Avastin in patients with wound dehiscence. The appropriate interval between termination of Avastin and subsequent elective surgery required to reduce the risks of impaired wound healing/wound dehiscence has not been determined. Discontinue at least 28 days prior to elective surgery. Do not initiate Avastin for at least 28 days after surgery and until the surgical wound is fully healed. [See Dosage and Administration (2.4), Warnings and Precautions (5.2), and Adverse Reactions (6.1).]
> Hemorrhage
> Severe or fatal hemorrhage, including hemoptysis, gastrointestinal bleeding, central nervous systems (CNS) hemorrhage, epistaxis, and vaginal bleeding occurred up to five-fold more frequently in patients receiving Avastin. Do not administer Avastin to patients with serious hemorrhage or recent hemoptysis. [See Dosage and Administration (2.4), Warnings and Precautions (5.3), and Adverse Reactions (6.1).]

I note that Genentech, with CDER's approval, has revised the Avastin labeling further since the time of the hearing to highlight additional side effect information:

- a new Warning subsection describing the increased risk of ovarian failure in premenopausal patients receiving bevacizumab and chemotherapy and recommendation that females of reproductive potential be informed of the increased risk of ovarian failure prior to starting treatment with bevacizumab,
- identification of osteonecrosis of the jaw as an adverse reaction of bevacizumab, and
- new information regarding the risks of venous thromboembolic events [VTEs] and bleeding in patients receiving anti-coagulation therapy after first VTE event while receiving bevacizumab.

adding Avastin to paclitaxel in this study increased the rate of other serious adverse events, as follows:

> Grade 3–4[21] adverse events occurring at a higher incidence (≥ 2%) in 363 patients receiving paclitaxel plus Avastin compared with 348 patients receiving paclitaxel alone were sensory neuropathy (24% vs. 18%), hypertension (16% vs. 1%), fatigue (11% vs. 5%), infection without neutropenia (9% vs. 5%), neutrophils (6% vs. 3%), vomiting (6% vs. 2%), diarrhea (5% vs. 1%), bone pain (4% vs. 2%), headache (4% vs. 1%), nausea (4% vs. 1%), cerebrovascular ischemia (3% vs. 0%), dehydration (3% vs. 1%), infection with unknown ANC (3% vs. 0.3%), rash/desquamation (3% vs. 0.3%) and proteinuria (3% vs. 0%).
>
> Sensory neuropathy, hypertension, and fatigue were reported at a ≥ 5% higher absolute incidence in the paclitaxel plus Avastin arm compared with the paclitaxel alone arm.[22]

The AVF2119g study was an open-label, multicenter, randomized trial evaluating Avastin in combination with capecitabine compared with capecitabine alone in 462 patients who had previously been treated with a taxane and anthracycline for breast cancer. The primary endpoint studied was PFS as determined by an independent review committee. There was no statistically significant difference in PFS between the treatment arms [HR 0.98 (95% CI 0.77, 1.25), p=0.86]. The median PFS was 4.2 months in the capecitabine arm and 4.9 months in the capecitabine plus Avastin arm. There was also no statistically significant difference in overall

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http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm274394.htm. Because this change occurred after the hearing, and Genentech did not have an opportunity to address the significance of this label change to the breast cancer indication for Avastin, I have not relied on this new information in making my decision in this proceeding.

[21] The severity of adverse events in the clinical trials submitted by Genentech was graded using the National Cancer Institute's ("NCI") Common Terminology Criteria for adverse events ("CTCAE"), v.2 and v.3.0 (Aug. 9, 2006), Docket No. FDA-2010-N-0621-0145, Appendix 14. "The CTCAE v3.0 displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline: Grade 1 Mild AE; Grade 2 Moderate AE; Grade 3 Severe AE; Grade 4 Life-threatening or disabling AE; Grade 5 Death related to AE." CTCAE v.3.0 at 1.

[22] Avastin Prescribing Information, 3. More detailed information regarding these adverse events is available on pages 5-7 of the prescribing information. Only Grade 3–5 non-hematologic and Grade 4–5 hematologic adverse events were collected in E2100.

survival, which was a secondary endpoint [HR 1.05 (95% CI 0.86, 1.30), p=0.63, log-rank test]. The ORR was higher with Avastin plus chemotherapy as compared to chemotherapy alone.[23]

CDER decided to refer Genentech's sBLA for the metastatic breast cancer indication to the Oncologic Drug Advisory Committee (ODAC) for advice on this supplemental application and the question whether PFS could constitute clinical benefit in the context of first-line treatments for metastatic breast cancer. The results of the E2100 and AVF2119g trials were presented to ODAC on December 5, 2007. Joint Statement ¶ 27.[24] After a thorough discussion of the evidence and the issues, ODAC members voted as follows at the December 5, 2007 meeting:

- Are the data provided sufficient to establish a favorable risk/benefit analysis for the use of bevacizumab plus paclitaxel for first-line treatment of patients with metastatic breast cancer? (Voting Question)

  Vote: Yes = 4 No = 5 Abstain = 0

Joint Statement ¶ 28.

B. Accelerated approval for Avastin's metastatic breast cancer indication

In a letter dated February 20, 2008, Genentech requested accelerated approval for use of Avastin in combination with paclitaxel for the first-line treatment of HER2-negative metastatic breast cancer. Joint Statement ¶ 29. As previously discussed, accelerated approval is available when FDA concludes there is some evidence that a drug will provide a clinical benefit that justifies its risk but there is not sufficient evidence to support a traditional approval. To verify clinical benefit for Avastin with metastatic breast cancer, Genentech proposed two clinical trials

[23] FDA Briefing Document for 2007 ODAC Meeting 23-24.
[24] Genentech and CDER agree that the transcript and summary minutes for this meeting faithfully and accurately report on the meeting. Joint Statement ¶ 27.

that it had already begun - AVADO and RIBBON1.[25] On February 22, 2008, CDER granted accelerated approval for the following indication:

> Avastin is indicated for the treatment of patients who have not received chemotherapy for metastatic HER2-negative breast cancer in combination with paclitaxel.
>
> The effectiveness of Avastin in MBC is based on an improvement in progression free survival. There are no data demonstrating an improvement in disease-related symptoms or increased survival with Avastin.
>
> Avastin is not indicated for patients with breast cancer that has progressed following anthracycline and taxane chemotherapy administered for metastatic disease.

Joint Statement ¶ 30, Attachment 1. CDER's approval letter stated that regular approval for the metastatic breast cancer indication was contingent upon successful completion of and submission of efficacy supplements containing the final reports and revised labeling for these studies. Joint Statement ¶ 33.

C. Submission of AVADO and RIBBON1 studies, and Genentech's request for regular approval

The AVADO study (BO17708) compared Avastin at two doses, plus docetaxel, to docetaxel alone. The RIBBON1 study (AVF3694g) consisted of two independently powered comparisons under a single protocol: Avastin plus taxane/anthracycline compared with taxane/anthracycline alone (where the taxane was docetaxel or nab-paclitaxel), and Avastin plus capecitabine to capecitabine alone. Joint Statement ¶ 17. As in E2100, PFS was the primary efficacy endpoint in these studies, and OS and ORR were secondary endpoints. Joint Statement ¶ 18. These were placebo-controlled, double-blinded trials, which were adequate and well controlled.[26] Genentech and CDER agree that the following table accurately summarizes efficacy data from the AVADO and RIBBON1 studies[27]:

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[25] Joint Statement ¶ 31. Genentech agreed that "[s]atisfactory review of the results of" these trials would be "required for the conversion of this accelerated approval" to regular approval. Letter from Dr. Todd W. Rich to Dr. Patricia Keegan, February 20, 2008, 1-2, , Docket No. FDA-2010-N-0621-0145, Appendix 13.
[26] Summary of Questions presented to the ODAC at the July 20, 2010 meeting.
[27] Joint Statement ¶ 19, Attachment 2.

Study Arm	Median PFS (months)	Median OS* (months)	ORR
AVADO			
Docetaxel + Avastin 15 mg/kg	8.8	30.2	63.1%
Docetaxel + Placebo	7.9	31.9	44.4%
Between-Arm Difference	0.9	−1.7	18.7%
Hazard Ratio (95% CI)	0.62 (0.48, 0.79)	1.00 (0.76, 1.32)	(9.0%, 28.4%)
	p = 0.0003	p = 0.98	p = 0.0001
Docetaxel + Avastin 7.5 mg/kg	8.7	30.8	55.2%
Docetaxel + Placebo	7.9	31.9	44.4%
Between-Arm Difference	0.8	−1.1	10.8%
Hazard Ratio (95% CI)	0.70 (0.55, 0.90)	1.10 (0.84, 1.45)	(0.9%, 20.7%)
	p = 0.0054	p = 0.48	p = 0.0295
RIBBON1			
Taxane/Anthracycline + Avastin	9.2	27.5	51.3%
Taxane/Anthracycline + Placebo	8.0	NR	37.9%
Between-Arm Difference	1.2	NR	13.5%
Hazard Ratio (95% CI)	0.64 (0.52, 0.80)	1.11 (0.86, 1.43)	(4.6%, 22.3%)
	p < 0.0001	p = 0.44	p = 0.0054
Capecitabine + Avastin	8.6	25.7	35.4%
Capecitabine + Placebo	5.7	22.8	23.6%
Between-Arm Difference	2.9	2.9	11.8%
Hazard Ratio (95% CI)	0.69 (0.56, 0.84)	0.88 (0.69, 1.13)	(3.4%, 20.2%)
	p = 0.0002	p = 0.33	p = 0.0097

* Updated OS analysis where available. CI = confidence interval; NR = not reached.

Survey data on quality of life were collected in the AVADO study, and did not show an improvement in quality of life.[28] Genentech and CDER also agree that the safety data observed in the AVADO and RIBBON1 studies were consistent with the safety profile of Avastin described in its approved prescribing information, and that the prescribing information is a fair and accurate description of Avastin's safety profile. Joint Statement ¶ 22, 23.

[28] The FACT-B instrument was used. Summary Minutes of the Oncologic Drugs Advisory Committee, July 20, 2010, 4; 2010 ODAC Meeting Tr. 99:3-6, 17-20.

Genentech submitted the results of the AVADO and RIBBON1 trials on November 16, 2009 in sBLA 125085/191 and sBLA 125084/192, respectively. In its submission, Genentech requested expansion of Avastin's labeling to include an indication for use in combination with docetaxel chemotherapy and with taxane-based, anthracycline-based or capecitabine chemotherapy for the first-line treatment of HER2-negative metastatic breast cancer. Joint Statement ¶ 36.

On July 16, 2010, Genentech also submitted the results of another trial of Avastin, the RIBBON2 trial (also referred to as the AVF3693g trial). RIBBON2 was a double-blind, placebo controlled, international trial conducted by Genentech to evaluate the safety and efficacy of Avastin in combination with taxanes, capecitabine, or gemcitabine in patients who have received prior chemotherapy for metastatic HER2-negative breast cancer.[29] Genentech submitted these results, together with the results of AVF2119g, to support an efficacy supplement seeking approval of Avastin in combination with taxanes, capecitabine or gemcitabine for use in patients who have received prior chemotherapy for metastatic HER2-negative breast cancer, as well as to support removal of a limitations of use statement from the INDICATIONS AND USAGE section (1.3) of the Avastin label. RIBBON2 showed a difference in median PFS of 2.1 months [HR of 0.78 (95% CI: 0.64, 0.93), p=0.0072], and no overall survival benefit.[30]

The trials were presented to ODAC on July 20, 2010.[31] Joint Statement ¶ 37. Based on their review of these trials and presentations made by CDER and Genentech, ODAC members voted as follows:

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[29] Note that this is a different class of patients than those in trials of patients that had not received prior chemotherapy for treatment of metastatic breast cancer.

[30] June 28 Tr. 168: 18-20; CDER Hearing Presentation Slide 78, Docket No. FDA-2010-N-0621-359.

[31] Genentech and CDER agree that the summary meeting minutes and transcript prepared for this meeting faithfully and accurately report on the meeting. Joint Statement ¶ 37.

- Does the addition of bevacizumab to docetaxel represent a favorable risk/benefit analysis for the initial treatment of patients with metastatic breast cancer?

  Vote: Yes = 0 No = 13 Abstain = 0

- Does the addition of bevacizumab to taxanes, anthracyclines, or capecitabine represent a favorable risk/benefit analysis for the initial treatment of patients with metastatic breast cancer?

  Vote: Yes = 1 No = 12 Abstain = 0

- Taking into consideration the totality of findings, and the responses to Questions 1 and 2 above, do the AVADO and RIBBON1 results provide confirmatory evidence of clinical benefit of bevacizumab in combination with paclitaxel for the initial treatment of metastatic breast cancer?

  Vote: Yes = 0 No = 13 Abstain = 0

- Should the indication for treatment of metastatic breast cancer be removed from the Avastin label?

  Vote: Yes = 12 No = 1 Abstain = 0.

Joint Statement ¶ 38.[32]

In response to feedback from the July 20, 2010 ODAC meeting, on August 16, 2010 Genentech submitted a summary of a proposed protocol for a study to characterize further the effect specifically of the combination of Avastin plus paclitaxel. The summary stated that the proposed study would include a prospective biomarker evaluation to try to identify patients who are more likely to derive a more substantial benefit from Avastin. Joint Statement ¶ 40.

D. Proposal to Withdraw Accelerated Approval

CDER scientists completed their review of the studies and Genentech's proposal, and determined that withdrawal of the accelerated approval was necessary. The final medical review leading to withdrawal was dated December 15, 2010. Consistent with the requirements of the

[32] Of the four ODAC members who voted that E2100 showed a positive risk-benefit profile based on the studies presented in 2007, two were still serving on the ODAC in 2010. Both of these ODAC members voted that AVADO and RIBBON1 failed to confirm benefit and that the metastatic breast cancer indication should be removed from the Avastin label. 2007 ODAC Meeting Tr. 278; 2010 ODAC Meeting Tr. 160.

accelerated approval regulations, 21 C.F.R. § 601.43(b), on December 16, 2010, the Director of CDER issued a Notice of Opportunity for a Hearing ("NOOH") on CDER's proposal to withdraw approval of Avastin's metastatic breast cancer indication. Joint Statement ¶ 42, 43.[33] The NOOH stated CDER's conclusion that AVADO and RIBBON1 failed to verify clinical benefit for Avastin in metastatic breast cancer and that Avastin is not safe or effective when used in accordance with its metastatic breast cancer indication. Joint Statement ¶ 44. On January 16, 2011, Genentech requested a hearing and submitted data analyses and information in support of its position that Avastin should "retain accelerated approval" for treatment of metastatic breast cancer in combination with paclitaxel, subject to Genentech's conduct of "a confirmatory study." Joint Statement ¶ 45.

E. The Hearing

The hearing procedures for the withdrawal of an accelerated approval for a biologic product are described in 21 C.F.R. § 601.43. This hearing was the first to be held pursuant to that provision.

FDA regulations provide a mechanism for the handling of hearings on matters such as withdrawals of regular drug approvals through a process that is referred to as "separation of functions," 21 C.F.R. § 10.55. This process is designed to assure that FDA hearings will provide a fair forum for discussion and resolution of the issues presented. The process takes advantage of the fact that FDA is organized with several Centers that are responsible for particular types of products, with a Commissioner's office that has responsibility for all regulated products. Thus, when separation of functions applies, the Commissioner's office acts in the role of a judge, while the product Center responsible for the decision being reviewed (here CDER) is one of the

[33] On August 27, 2010, at CDER's request, Genentech ceased affirmative marketing of Avastin for metastatic breast cancer. Joint Statement ¶ 41. On December 16, 2010, CDER issued two complete response letters on Genentech's November 16, 2009 sBLA submissions of the AVADO and RIBBON1 results. *Id.* at ¶ 42.

hearing participants, together with the applicant who is opposing that Center's action. Separation of functions requires that any communication between the Center that is a party in the hearing or the applicant and the Commissioner's office (including the presiding officer) concerning the subject of the hearing be on the record and not *ex parte*. Similarly, the Commissioner's office is not to communicate with others concerning the subject of the hearing in a manner that is not on the record.[34] While section 601.43(d) states the separation of functions does not apply to hearings on withdrawal of accelerated approvals, FDA decided to follow the separation of functions policy with respect to this hearing as a prudential matter given the significant public interest in the matter.[35]

Section 601.43(e)(1) requires an advisory committee be present at the hearing, review the issues involved, and provide advice and recommendations to the Commissioner. FDA interprets this regulation, consistent with the preamble to the proposal that became the regulation, 57 Fed. Reg. 13234 (Apr. 15, 1992), to require the participation of the standing advisory committee that advises the review division on the drug in question. In this case, that was the ODAC.[36] While FDA could have added consultants to the advisory committee for this proceeding, we faced the reality that many experts in this area have already expressed a view on this issue and/or might be considered as having conflicts because of their association with one of the parties to the hearing or with competitors to Genentech. Thus, we recognized the possibility that a decision to add

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[34] When separation of functions applies, all employees and officials of the Center that is a party in the hearing are considered to be on the Center's "team" unless the Commissioner specifically designates those persons on the public record as being available to assist her with respect to the hearing. In this case, one CDER physician was assigned to assist the Commissioner with respect to conflict of interest evaluation of advisory committee members, and several CDER employees whose job is to handle logistics and communication with respect to the CDER advisory committee were assigned to the Commissioner's team. These assignments were documented in the public record.

[35] I note that this does not necessarily create a precedent for other such hearings in the future.

[36] It is important to note that the role of the advisory committee in this hearing was to ask questions and then provide its advice and recommendations to me. Ultimately, it is my responsibility to decide the issues presented on the basis of the evidence. The vote of the advisory committee members, which as discussed below was unanimously in favor of withdrawal of approval, does not constrain me to agree with the position that they adopted.

consultants to the advisory committee would itself have been the subject of dispute between the parties. Accordingly, we concluded that the best way to obtain the advice of experts on these issues is for the parties to present those experts at the hearing itself and did not add consultants to the advisory committee. In fact, Genentech did present its preferred expert, Dr. Joyce O'Shaughnessy, at the hearing. The transcript reflects that Dr. O'Shaughnessy not only presented her views, but was consulted by members of the advisory committee during that committee's deliberations on the second day of the hearing.[37]

I appointed Dr. Karen Midthun, who serves as the Director of the Center for Biologics Evaluation and Research, and is an experienced medical product reviewer, to be the presiding officer at the hearing. By letter dated February 23, 2011, Dr. Midthun advised the parties that FDA was granting the hearing request. In order to focus the hearing on the issues requiring resolution, Dr. Midthun directed counsel for Genentech and CDER to consult together and to prepare a joint statement of those facts that were not in dispute and of those issues that were disputed. The joint statement, submitted on April 7, 2011, was useful in establishing the areas of factual agreement and is cited at various points in this decision. While the parties could not agree on the wording of the issues for decision and presented separate documents stating their different views on April 8, 2011, in general those statements reflected the standard set out in the regulation and statute and were not significantly different in substance from the issues identified in the notice of hearing. That notice was issued on May 6, 2011, and subsequently published in the Federal Register, 76 Fed. Reg. 27332 (May 11, 2011).

The notice of hearing specifically addressed one issue raised by the parties in their preliminary filings. Genentech had proposed to raise issues concerning the consistency of

[37] Genentech had originally identified an additional non-company expert, Dr. Howard Burris, as a witness at the hearing, but ultimately decided not to have Dr. Burris participate.

CDER's position with respect to Avastin with CDER's decisions with respect to other products for the treatment of metastatic breast cancer or of other products approved under the accelerated approval program. As the notice stated, issues with respect to FDA action on other products are not relevant to this proceeding. Each decision to withdraw or not to withdraw the approval of a product must be made on its own merits. If the decision with respect to another product is in error, that would not justify continuing that error with respect to the metastatic breast cancer indication for Avastin. *See Edison Pharm. Co., Inc. v. Food and Drug Admin.*, 600 F.2d 831, 843 (D.C. Cir. 1979). Moreover, the notice recognized that, as a practical matter, it would not be possible to evaluate the different circumstances associated with decisions with respect to other products[38] in the context of this or any hearing. Nevertheless, Genentech did make some arguments concerning other approvals and I will, for completeness, address those arguments later in this decision.

While Dr. Midthun had originally taken the position that interested persons other than the two parties to the hearing would be permitted to submit their views only in writing, she ultimately concluded, and I agreed, that it was appropriate to set aside time at the outset of the hearing to permit members of the public to provide oral testimony. That testimony, in many cases, expressed the strongly held belief that Avastin had helped particular individuals. In other cases, members of the public argued that the Avastin approval should be withdrawn.

On May 17, 2011, CDER and Genentech each submitted a summary of the evidence and arguments that they intended to present at the oral hearing. That hearing was held on June 28

[38] As previously noted, a decision on safety and effectiveness of a drug will depend on, among other considerations, the measure of effectiveness proposed, including, when PFS is used, hazard ratios and increase in median PFS, whether there is any evidence of effectiveness by other measures, such as overall survival or reduction in symptoms, levels of confidence in the clinical trials and their consistency, considerations of the toxicity of the drug compared to its potential benefit in the patient population for which it is intended.

and 29 at the FDA's White Oak facility. The hearing was open to the public and a webcast was made available to those who did not attend in person.

This is how the hearing was structured: First, the public presenters made their presentations. Thereafter, a panel of presenters from CDER was given two hours to explain CDER's reasons for the proposed withdrawal. There was then a one-hour opportunity for representatives of Genentech to ask questions of the CDER presenters. After that, there was a one-hour opportunity for Dr. Midthun and members of the advisory committee to ask questions of the CDER presenters. There was then an opportunity for CDER representatives to ask the CDER presenters any clarifying questions. This ended the first day of the hearing.

On the second day there was a two hour opportunity for Genentech witnesses to present the reasons they believed the approval should be continued. CDER representatives then had a one-hour opportunity to ask questions of the Genentech presenters, followed by a one-hour opportunity for Dr. Midthun and members of the advisory committee to ask questions of the Genentech presenters, followed by an opportunity for Genentech representatives to ask the Genentech presenters clarifying questions. There was then a discussion of the issues by members of the advisory committee, who ultimately voted on each of the issues.[39]

As noted, at the conclusion of the hearing, the advisory committee members were asked for their advice and recommendations, and they voted as follows:

- Question 1. Do the AVADO and Ribbon 1 trials fail to verify the clinical benefit of Avastin for the breast cancer indication for which it was approved?

  Vote: *Yes = 6* *No = 0* *Abstain = 0*

[39] There were seven members of the advisory committee, six of whom were voting members. The seventh was the industry representative. As noted, the advisory committee members included Dr. O'Shaughnessy in their discussion. They also asked some questions of representatives of Genentech and CDER.

- Question 2(a). Does the available evidence on Avastin demonstrate that the drug has not been shown to be effective for the breast cancer indication for which it was approved?

  Vote: *Yes = 6* *No = 0* *Abstain = 0*

- Question 2(b). Does the available evidence on Avastin demonstrate that the drug has not been shown to be safe for the breast cancer indication for which it was approved and that Avastin has not been shown to present a clinical benefit that justified the risks associated with use of the product for this indication?

  Vote: *Yes = 6* *No = 0* *Abstain = 0*

- Question 3. If the Commissioner agrees with the grounds for withdrawal, set out in Issue 1, Issue 2(a), or Issue 2(b), should FDA nevertheless continue the approval of the breast cancer indication while the sponsor designs and conducts additional studies intended to verify the drug's clinical benefit?

  Vote: *Yes = 0* *No = 6* *Abstain = 0*

After the hearing, CDER and Genentech were originally permitted until July 14, 2011 to submit a summary of their views as to what had been shown in the hearing. At the request of CDER and Genentech, this deadline was first extended to July 28, 2011 and then, at Genentech's request, it was extended again to August 4, 2011. FDA also decided to leave the docket open pending the submission of the parties' statements. The docket closed to CDER, Genentech, and the public on August 4, 2011, and at that point, the record for this proceeding closed. The record consists of the record made of the hearing (a video is available on the FDA website at http://www.fda.gov/NewsEvents/MeetingsConferencesWorkshops/ucm255874.htm) and materials in the public docket, which includes submissions by the parties and the public, and correspondence with the Presiding Officer regarding this matter.

V. THE CONDITIONS FOR WITHDRAWING APPROVAL OF THE METASTATIC BREAST CANCER INDICATION HAVE BEEN MET

The first question that I addressed is whether either of the two grounds that CDER has proposed for withdrawing the application had been met. After careful review of the record, I conclude that both conditions have been met. The record reflects that when Avastin was submitted for approval of the metastatic breast cancer indication, there was evidence in E2100 suggesting an effect on PFS that might constitute clinical benefit, but this was only one study, and there were questions as to whether this study had accurately characterized Avastin's effect in the metastatic breast cancer context. Accordingly, and in light of well established safety risks associated with Avastin, CDER granted only accelerated approval, conditioned on confirmatory tests to verify a clinical benefit large enough to justify exposing patients to the drug. As results from these studies have come in, they have substantially changed the profile of this drug. AVADO and RIBBON1 have not verified the clinical benefit shown in E2100, and considering all the evidence, I cannot conclude that Avastin has been shown to be safe and effective for the metastatic breast cancer indication.

A. The confirmatory studies that Genentech submitted do not verify clinical benefit.

Clinical benefit refers to a benefit that is meaningful to a patient. It is different than a clinical endpoint, which is simply an outcome that is the subject of study, which may or may not be meaningful to the patient depending on the benefit conveyed and the risks of the therapy.

FDA's accelerated approval for Avastin's metastatic breast cancer indication was based on the results of the E2100 study, which did not demonstrate an overall survival benefit or

improvement in quality of life for patients with metastatic breast cancer,[40] but did show an improvement in PFS in patients who were treated with the combination of Avastin plus paclitaxel as compared to paclitaxel alone. The increase in median PFS shown in this trial for patients in the Avastin plus paclitaxel arm was 5.5 months [hazard ratio 0.48 (95% CI (0.39-0.61)], which CDER concludes would represent clinical benefit for this indication if benefit of similar magnitude could be confirmed. However, in light of the known toxicities of Avastin and the risk of serious and life-threatening reactions to the drug, regular approval depended on confidence in the magnitude of PFS effect.

By itself, E2100 left a number of questions about whether the magnitude of treatment effect on PFS had been accurately described. It was only one study, and it did not show a gain in overall survival, as might be expected if its report of relatively substantial PFS gains was accurate. There were also methodological questions. A significant number of patients were lost to follow-up before the treatment effect on PFS could be confirmed, and so data were missing from the final analyses. Also, some disagreements were noted between initial measurements of tumor progression in this open-label trial and the independent review that was done later to confirm them. Although these methodological concerns were mitigated by independent review and careful analysis of the study data, which persuaded CDER that E2100 had shown an effect for Avastin on PFS, uncertainty about the magnitude of benefit remained. For example, although a sensitivity analysis conducted to estimate the effect of missing data on the reported PFS results showed a significant difference favoring the Avastin arm, estimates of the PFS difference varied

[40] Avastin Prescribing Information ("The effectiveness of Avastin in [metastatic breast cancer] is based on an improvement in progression free survival. There are no data demonstrating an improvement in disease-related symptoms or increased survival with Avastin."). *See also* June 29 Tr. 171:9-12 (statement by Dr. Horning: "[W]e do not have quality of life data that meet CDER's standards from our first-line metastatic breast cancer trials").

according to assumptions about the nature of the missing data, ranging from a median PFS gain of 5.5 months (HR 0.48) to a median PFS gain of 2.4 months (HR 0.78).[41]

As previously discussed, as part of its sBLA, Genentech had submitted a study of Avastin plus capecitabine in metastatic breast cancer patients undergoing second-line treatment, AVF2119g, which did not show improvement in PFS, OS, or quality of life compared to capecitabine alone. Because AVF2119g had enrolled patients receiving second-line treatment, the results must be interpreted with care; such patients can be less responsive to treatment than patients receiving first-line treatment, and that may contribute to a less impressive result. After careful evaluation, CDER was unable to conclude that the difference with regard to Avastin's effect on PFS between E2100 and AVF2119g was due entirely to the difference in patient population. When the sBLA for the metastatic breast cancer indication was referred to the ODAC in 2007, its members split 5-4, with the majority voting that E2100 had not established a favorable risk-benefit analysis for use of Avastin with paclitaxel for first-line treatment of patients with metastatic breast cancer.[42]

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[41] CDER and Genentech dispute the significance of the methodological issues that CDER has raised regarding E2100. CDER has noted a number of issues, including missing scans in 10 percent of the patients; failure to follow 34 percent of the patients until an independent review determined a PFS event or end of study; lack of reliability in the determination of radiographic disease progression and the date of progression between the independent radiologist and study investigators...," and an "incomplete assessment of toxicities." June 28 Tr. 148:5-22; CDER Hearing Presentation Slides 26-27. Genentech argues that E2100 was well-designed and conducted, and points out that it took extensive steps to address the issues CDER raised- including multiple sensitivity analyses to determine the effect that missing data could have had; independent confirmation of scan interpretations, and assessment to test for possible bias; and assessment for possible bias from the fact that reported results of E2100 were based on an interim analysis. Genentech Post-Hearing Submission 15-19. Genentech argues that these additional evaluations found no bias, that E2100 was in line with other studies used to support approval, and that CDER had recognized E2100 demonstrated a robust effect and bias seemed unlikely. *Id.* I conclude that E2100 demonstrated an effect on PFS but did not conclusively establish its magnitude. The sensitivity analyses showed a range of effects on PFS and CDER concluded that there was definitely an effect on PFS, but was uncertain about the magnitude of the effect, especially in light of the failure to demonstrate an effect on PFS in AVF2119g. This uncertainty, particularly in light of the fact that an effect had been shown in only one trial, led to accelerated approval, requiring confirmatory studies.

[42] Joint Submission ¶ 37.

The Eastern Cooporative Oncology Group submitted a comment to the docket defending the quality and significance of E2100[43], and neither CDER nor I dismiss this study. It is undeniable, however, that this single study cannot be considered dispositive. Confirmation of the results that it reported was necessary, which is why Avastin was given accelerated rather than regular approval for the metastatic breast cancer indication.

As noted, to confirm the benefit of E2100, Genentech proposed two studies that were already underway, AVADO and RIBBON1. These studies tested combinations of Avastin with chemotherapy drugs other than paclitaxel, and were submitted not only to convert the Avastin-plus-paclitaxel approval into regular approval, but also to support a broad, taxane-based approval for Avastin, as well as approval for use in combination with docetaxel, taxane-based, anthracycline-based or capecitabine therapy.[44] The trials also showed that Avastin had a statistically significant effect on PFS, but the magnitude of this effect was much reduced. In AVADO, the improvement in median PFS at Avastin 7.5 mg/kg dosage, in combination with docetaxel, was 0.8 months [hazard ratio (HR) of 0.70 (95% confidence interval ("CI"): 0.55, 0.90), p=0.005], and the improvement at the Avastin 15 mg/kg dosage, in combination with docetaxel, was 0.9 months [HR 0.62 (95% CI: 0.48, 0.79), p<0.0003]. In RIBBON1, the improvement in median PFS in the Avastin plus anthracycline/taxane cohort was 1.2 months (HR 0.64 (95% CI: 0.52, 0.80), p<0.0001), and in the Avastin plus capecitabine cohort it was 2.9 months (HR 0.69 (95% CI: 0.56, 0.84), p <0.0002).[45] As in E2100, the studies also did not demonstrate that adding Avastin to chemotherapy provided a benefit to overall survival, and

[43] Docket No. FDA-2010-N-0621-0468.
[44] Joint Statement, ¶ 36. Genentech suggested a broad taxane-based approval despite the fact that the best results in the confirmatory studies were when Avastin was used in combination with a non-taxane drug, capecitabine.
[45] Joint Statement, Attachment 2. As noted above, ORR differences were also substantially smaller than in E2100.

patient responses to questionnaires in the AVADO study did not demonstrate an improvement in quality of life.[46]

When these data were presented to the ODAC in 2010, the committee's view was that a favorable risk-benefit analysis had not been established for Avastin with any of the chemotherapy partners for which Genentech was seeking an approval (13-0 and 12-1); that the studies failed to verify clinical benefit for the Avastin plus paclitaxel indication (13-0); and that the metastatic breast cancer indication should be removed from product labeling (12-1).[47] Notably, of the four ODAC members in 2007 who voted that E2100 had established a favorable risk-benefit analysis, two were still serving on the ODAC in 2010; in light of the new studies, both changed their views and voted that clinical benefit was not verified and that the metastatic breast cancer indication should be removed from the Avastin labeling.[48] CDER, as noted, has also proposed to withdraw the indication on grounds that clinical benefit has not been confirmed.

I agree with CDER's position on this issue. Genentech's confirmatory trials failed to confirm the magnitude of effect on PFS that was shown in E2100, or show an improvement in OS benefit or quality of life. While the confirmatory studies did show a small effect on PFS, as seen from the hazard ratios reported, simply showing an effect cannot be considered to confirm

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[46] June 29 Tr. 143:21-144:3 ("Dr. Jenkins: So you would agree with the statement that there is no demonstrated overall survival advantage for Avastin in first-line metastatic breast cancer? Dr. Reimann: Yes."); June 29 Tr. 177 (Dr. Barron: "It's absolutely true that there was no statistically significant improvement in overall survival in E2100."). 2010 ODAC Meeting Tr. 99: 21-22 (Dr. Horning: "[W]e do not have any difference in patient-reported outcomes.").

[47] Joint Statement ¶ 38. *See also* 2010 ODAC Meeting Summary Minutes 4-7. The ODAC member who indicated that she supported leaving the indication on Avastin's labeling explained that this was only because the labeling stated that "There are no data demonstrating an improvement in disease-related symptoms or increased survival with Avastin." 2010 ODAC Meeting Tr. 226:22-227:1.

[48] *See* 2007 ODAC Meeting Tr. 278; 2010 ODAC Meeting Tr. 160:4-13 (Dr. Mortimer: "I argued at [the 2007 ODAC meeting] that a doubling in response rate was an incredible improvement and that furthermore doubling the progression-free survival was also an amazing finding especially in the setting of a cooperative group trial, which, you know, if anything might be a little harder to prove. So I looked forward to this meeting to see what the advantages ultimately turned out. I have to say, I'm very disappointed that in fact it did not support the reasons that I argued so strongly in favor of the drug previously."); *id.* at 231:7-8 (Dr. Lyman: "[T]hese studies didn't fully live up to the E2100 data.").

clinical benefit for Avastin. Given the known toxicities of Avastin - which include risk of gastrointestinal perforation, wound-healing problems, serious hemorrhage, and other serious side effects (see prescribing information above at n.20, and discussion in section V.B.2.) - the diminished evidence of improvement of PFS combined with the demonstrated risk does not confirm the presence of clinical benefit. I conclude that the standard for withdrawal has been satisfied because clinical benefit has not been confirmed, and when this study is viewed in the light of the confirmatory trials, the evidence does not show that Avastin has had an effect on PFS large enough to constitute clinical benefit. The early promise suggested by E2100 has not been verified.

Genentech concedes that the magnitude of benefit shown in the confirmatory studies was less than in E2100, but argues that the confirmatory studies verify clinical benefit because they achieved their primary endpoint of showing a statistically significant effect on PFS, and that the benefit can be seen in the robust hazard ratios reported by the trials.[49] However, a statistically significant effect on a clinical endpoint does not, by itself, demonstrate meaningful benefit to a patient. The difference between treatment and control arms must be not only statistically significant (meaning, not likely owing to chance) but also large enough to be meaningful to a patient. And as noted above, the magnitude of effect on PFS shown in the confirmatory studies and RIBBON2 was disappointingly small. And, while hazard ratios are useful measurements, and are certainly part of risk-benefit analysis, it is not appropriate to assess a drug's magnitude of benefit by looking at hazard ratios alone. The reason is that a hazard ratio is a measure of relative risk: it compares the risk over a period of time that patients in the treatment arm will experience a negative event (tumor growth or death) against the risk that the same event will happen to patients in the control arm. To be interpreted correctly, it is generally necessary to

[49] *See, e.g.*, June 29 Tr. 8:18-21; 12:16-21.

also consider a measure of absolute difference. This is because the hazard ratio may be statistically significant, even if there is very little absolute difference between two groups. As CDER's statistician Dr. Sridhara explained, it would be possible to run two trials, each of which showed a hazard ratio of 0.5, when even though in one trial a drug was associated with a two-month increase in median PFS and in the other trial with a 12-month increase in median PFS.[50] Dr. Sridhara also explained: "we have had applications where the hazard ratio was .5 and, in fact, the difference in PFS was just two weeks. ... [T]he hazard ratio was small enough, but the difference in medians was too small to be clinically meaningful."[51] For example, in the case of Avastin, the hazard ratios were statistically significant not only with E2100, where the absolute gain in median PFS was notable, but also with AVADO, where Genentech concedes the magnitude of the PFS gain was much smaller.

It is for this reason that FDA-approved labeling informs prescribers of both absolute and relative differences in treatment effects, and of course, why the approved labeling for Avastin's metastatic breast cancer indication has also included both the absolute difference in median PFS as well as the relative risk reduction, expressed as the hazard ratio.[52] Even Genentech agrees, as a general matter, that it is necessary to look at both hazard ratio and absolute magnitude of effect

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[50] June 28 Tr. 242:12-16 ("[A] change in two months to four months [an improvement of 2 months] versus a change in 12 months to 24 months [an improvement of 12 months], under certain assumptions, you can say that the hazard ratio is .5 in both cases.") Generally, when the risk of an event is the same in both the treatment and control arm, the hazard ratio will be expressed as 1; when the risk in the treatment arm is lower than in the control arm, the hazard ratio will be less than 1.

[51] June 28 Tr. 243:17-19.

[52] Avastin Prescribing Information 14; Guidance for Industry: *Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products -- Content and Format* 8 (January 2006), available at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127534.pdf ("When presenting differences between study group and comparator, it is important to present the absolute difference between treatment groups for the endpoint measured, as well as the relative difference (e.g., relative risk reduction or hazard ratio). ... In most cases, the treatment effect is presented as a mean or median result accompanied by a measure of uncertainty or distribution of results for the treated groups.)

to evaluate Avastin's effect,[53] and of course, it has on several occasions recognized impact on median PFS as an appropriate measure of magnitude of effect. For example, Genentech's experts underscored the importance of improvement in median PFS in making their presentation to the ODAC in 2007, and the company prominently featured the median PFS difference shown by E2100 in its advertising materials for Avastin.[54] I note that Genentech agrees that the magnitude of benefit shown in AVADO (median PFS gain 0.8 or 0.9 months, HR 0.62 or 0.70) is less than the benefit shown in the capecitabine arm of RIBBON1 (median PFS gain 2.9 months, HR 0.69) even though the hazard ratios are in a similar range. Although Genentech argues that CDER has focused "solely" on the difference in median PFS, it is clear that CDER has considered both hazard ratio and measures of absolute magnitude in making its determination, and Genentech has not identified any other measure of absolute benefit that would lead to a materially different view of the efficacy data.

I conclude that the confirmatory studies did not in fact confirm the clinical benefit that appeared in the E2100 trial. Genentech's argument, ultimately, is that some lesser benefit than that seen in the E2100 trial should be considered to confirm the clinical benefit. Whether or not some benefit less than suggested by E2100 would be adequate, I conclude that the lesser benefit shown in the confirmatory trials presented by Genentech does not justify the risks associated with this drug in this patient population.

Genentech has made several other arguments, discussed in more detail below, that could be considered relevant to the question of whether clinical benefit has been confirmed, as well as

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[53] *See, e.g.*, June 29 Tr. 140:16-20 (Dr. Jenkins asked: "[H]ow can I put a hazard ratio into perspective without looking at the magnitude of the median difference in progression-free survival?" Dr. Reimann answered: "You can't. You need to look both at hazard ratio and absolute benefits.").

[54] CDER Hearing Presentation Slide 97 (reproducing Genentech advertising materials); 2007 ODAC Meeting Tr. 89:5-8, 16-21 (statement of Genentech's expert, Dr. Winer) ("[F]or progression-free survival to equal benefit, for it to be meaningful, this progression-free survival needs to be substantial in magnitude.... In terms of the magnitude of the benefit, as you've heard now multiple times, the improvement in outcome in terms of progression-free survival is substantial with a hazard ratio of. 48 and an absolute improvement of 5-1/2 months.").

to the questions discussed in the following sections of whether Avastin has been shown to be safe and effective for its metastatic breast cancer indication and whether I should, as a matter of discretion, continue accelerated approval. Because, for the reasons explained below, I ultimately do not find any of those arguments convincing, I do not find them to be a basis for a conclusion that the clinical benefit that had been suggested by the E2100 results has been confirmed.

B. The available evidence demonstrates neither that Avastin has been shown to be effective for the treatment of metastatic breast cancer, or that it has been shown to be safe for that use

1. Avastin has not been shown to be effective for its metastatic breast cancer indication

For similar reasons, when I turned to the second issue presented, I also find that the risk-benefit analysis for this drug, in light of all the evidence, is not positive. If the FDA had before it, at the time of the initial decision on accelerated approval, all of the data that now are available, we could not have found that this drug was shown to be effective for the metastatic breast cancer indication. The evidence that use of this drug for this purpose provides any meaningful benefit to patients is weak and the evidence that use of the drug by metastatic breast cancer patients will harm some of those patients is undeniable.

Genentech has made an argument concerning the significance of the confirmatory studies that goes to the effectiveness of Avastin for treatment of metastatic breast cancer.[55] It argues that the less robust results observed with respect to studies other than E2100 are explainable because there is some synergy between Avastin and paclitaxel. Genentech contends that the "most plausible" explanation for the discrepancy between E2100 and the other trials is that Avastin is

[55] I discuss this argument with respect to issue two, as it would not seem to support the position that the additional trials had confirmed the clinical benefit suggested by the E2100 trial. At most, it would be a reason why those results could be considered not to disprove the results of the E2100 trial. Nevertheless, I have also considered whether this preferred-partner hypothesis would lead to the conclusion that the conditions for withdrawal are not satisfied; I conclude it does not.

more effective when paired with paclitaxel than with other chemotherapy agents. Specifically, Genentech hypothesizes that the Avastin-paclitaxel combination performed better because it was better tolerated by patients than the other combinations and administered on a more frequent and intense dosing schedule, which meant patients had "greater exposure to both a highly potent chemotherapy and the anti-angiogenic activity of Avastin." Genentech Post-Hearing Submission 21.

Genentech recognizes, however, that its hypothesis is far from proven. It has noted that "the scientific basis for the observed differential effect with paclitaxel is not yet understood," and that its hypothesis is only one of "multiple hypotheses [that] can be generated for why a differential effect would be observed with distinct chemotherapy partners."[56] There are clearly not data to establish this hypothesis, and some of the data that are available are not supportive. As CDER has pointed out, Genentech has not presented evidence of drug interactions or antagonism between Avastin and chemotherapy drugs other than paclitaxel to support this theory. Antagonism would be shown if the treatment effect of Avastin plus other chemotherapy agents, when they are given in combination, were smaller than the sum of the treatment effects when each drug is given alone. Synergism would be shown if the treatment effect of Avastin and paclitaxel taken together were greater than the effect when each is taken alone. Studies to test for these relationships are well known, and are commonly used to test hypotheses similar to the ones Genentech advances here. Genentech has not performed such studies, or if it has, it has not submitted them to FDA. The available evidence is to the contrary. CDER has conducted

[56] Submission of Genentech, Inc. in Response to the Food and Drug Administration's Notice of Opportunity for Hearing and Proposal to Withdraw Approval of AVASTIN® (Bevacizumab) in Combination with Weekly Paclitaxel for the First-Line Treatment of Patients with Metastatic Breast Cancer 3, 28, Docket No. FDA-2010-N-0621-0002.

exploratory analysis of the AVADO and RIBBON1 data to look for evidence of interactions between Avastin and the chemotherapeutic agents, and did not find them.[57]

Other studies with Avastin are also not consistent with the hypothesis that length of treatment correlates with treatment effect. In studies of Avastin with colorectal cancer, lung cancer, and renal cell cancer, Avastin showed improved survival or PFS even though treatment length was limited by protocol.[58] Genentech does not propose to design a study that could test its duration-of-treatment hypothesis.

In further support of its preferred-partner argument, Genentech notes that CDER approved Avastin only for use with paclitaxel, and argues that when CDER made this decision, it "implicitly recogniz[ed] that the chemotherapy partner affected the efficacy results observed in the different studies."[59] However, CDER indicates that this did not reflect a "general policy to consider each drug combination a distinct experiment that cannot be generalized," and does not indicate that CDER believed a differential effect among chemotherapy partners had been established.[60] Rather, these decisions reflected uncertainty about how to interpret the difference in the outcomes of the E2100 and AVF2119g trials.[61] A differential effect based on chemotherapy partners was one possible explanation, but this was by no means proven and to the extent a difference between partners might exist, the magnitude of any such difference was not defined. CDER's account seems entirely reasonable, and it is difficult to understand why CDER

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[57] June 28 Tr. 182:4-183:12. *See also* the four clinical pharmacology reviews submitted by CDER as exhibits 9-12 of its Post-Hearing Submission.

[58] June 28 Tr. 183:13-184:7. Genentech has put forth a hypothesis that longer duration of therapy leads to better outcome but, until that hypothesis is tested (i.e., a study is conducted to test it), it remains a hypothesis and does not provide the evidence that is necessary to support a decision to continue accelerated approval.

[59] Genentech Post-Hearing Submission 23. Genentech also quotes the minutes of the January 10, 2006 meeting with CDER, which indicate that one reason for the design of the RIBBON1 study was that "the treatment effect will vary according to the chemotherapy regimen used." Genentech Post-Hearing Submission 23.

[60] "Summary of Arguments Supporting CDER's Proposal to Withdraw Approval of Avastin's Indication for the Treatment of Metastatic Breast Cancer" (hereafter, CDER Summary of Arguments) 39, Docket No. FDA-2010-N-0621-0144.

[61] *Id.*; *see also* June 28 Tr., 254-55.

would have accepted AVADO and RIBBON1 as confirmatory studies (or why Genentech would have proposed them) if it was not thought that the results could be generalizable. Genentech, at the time that Avastin received accelerated approval, and up to the time CDER proposed to withdraw approval for the metastatic breast cancer indication, argued that the results of E2100 lent support to a broad, taxane-based indication for Avastin. For example, it stated in supplement STN BL 125085/91 section 2.5.1 at 8 that "all taxanes, at either of the two common schedules, are frequently used in the treatment of metastatic breast cancer because the literature supports considering taxanes as a class of cytotoxic agent based on their similar efficacy and safety in the treatment of metastatic breast cancer."[62]

Ultimately, I do not find that there is evidence of a preferred-partner relationship between Avastin and paclitaxel sufficient to overcome the negative results of AVADO and RIBBON1 and I do not find that the E2100 results alone, or together with the other data that have been submitted, demonstrate that Avastin is effective when utilized with paclitaxel.

Another argument raised in connection with the hearing that might be said to address the effectiveness of Avastin for its metastatic breast cancer indication[63] is the contention that, whatever its effect on most patients, Avastin is shown to be effective for a group of "super responders." A few women with metastatic breast cancer who have taken Avastin together with other chemotherapeutics have reported experiences that are much better than the norm, and some of them testified at the hearing about their improvement after they began on a combination Avastin-chemotherapy treatment.[64] Others gave testimony about family and friends, or

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[62] STN BL 125085/91 section 2.5.1 at 8, quoted in CDER Summary of Arguments at 39.

[63] Again, this argument, even if accepted, would not seem to support the Genentech position that the clinical benefits suggested by E2100 have been confirmed. Those benefits, which were the basis for the accelerated approval, were shown for the test population as whole.

[64] In some cases, that therapy was apparently in combination with drugs other than paclitaxel, which is covered by the approval at issue here.

submitted comments to the docket. It is clear that many people feel strongly about this issue, or are convinced that some women are in fact "super-responders" to Avastin.

I have been moved by these stories. But I am also mindful of other complicating factors that make it difficult to draw conclusions from these stories alone. Patients who take Avastin are generally also taking a chemotherapy agent, as was true of all the patients in the trials, and their success may be attributable to the other agent. There is also often considerable variation in the natural history of this disease, from patient to patient, which we are not always able to predict or explain. And, of course, while some patients have better-than-average results on Avastin or chemotherapy, others have poor results or are even seriously harmed. It is often difficult to determine which of these factors is responsible for a particular outcome, and this is why applicants are required to run clinical trials to compare, as best they can, the effect that two different treatments will have. When we compare the survival and PFS curves of patients in the control arms and Avastin arms of the trials that Genentech has submitted, we do not find that Avastin has demonstrated a meaningful PFS or OS advantage, and it is not possible to determine if there is some subset of patients within the population as a whole that may have had a meaningful benefit.[65]

Genentech has proposed a new clinical trial that might identify a subset of patients for whom Avastin plus paclitaxel would present a positive benefit-risk calculation, and I will discuss that proposal below when I address the request that I extend the accelerated approval as a discretionary matter. At this point, however, there are simply not convincing data to show that Avastin plus paclitaxel is effective for all or even some patients who suffer from metastatic breast cancer.

[65] *See, e.g.*, June 28 Tr. 228:8-11; 300:10-302:17.

I have discussed above the two confirmatory trials upon which Genentech principally relies. In addition to the confirmatory trials, Genentech submitted another trial of Avastin with capecitabine in second-line treatment of metastatic breast cancer - RIBBON2 - which showed a median PFS gain of only 2.1 months, [HR of 0.78 (95% CI: 0.64, 0.93), p=0.0072], and no overall survival benefit. Including RIBBON2, there have been five studies of Avastin submitted to FDA in support of the indication for metastatic breast cancer, involving more than 3,500 patients.[66] None of these studies has demonstrated an overall survival benefit or an improvement in quality of life, and none of the four studies, AVADO, RIBBON1, AVF2119g and RIBBON2, has come close to replicating the PFS gain shown in E2100.

Genentech has suggested that some observed differences in mortality, which do not reach the level of statistical significance, may nevertheless suggest a trend of OS benefit. I conclude that these do not change the risk-benefit determination or my judgment regarding clinical benefit.

First, Genentech pooled the safety data across E2100, AVADO, and RIBBON1, and noted that across these trials there were 3.8% fewer total deaths and 3.4% fewer deaths related to metastatic breast cancer, and deaths attributable to treatment were identical, at 1.8%.[67] However, even if the exploratory analysis of these pooled data is accepted, it does not offer evidence of OS benefit. The difference in median survival is one-third of a month (median survival of 26.7 months for the Avastin plus chemotherapy group vs. 26.4 months for the chemotherapy group), and this difference falls well short of statistical significance: the hazard ratio across the two

[66] June 28 Tr. 207:2-6.
[67] Genentech Post-Hearing Submission 28-29; June 29 Tr. 20:2-10; Genentech Hearing Presentation Slides 21, 26, Docket No. FDA-2010-N-0621-0424.

groups is 0.97 (95% confidence interval of 0.86 - 1.08), and a p-value of 0.56.[68] In fact, the confidence interval includes the possibility that use of Avastin would reduce overall survival.

Moreover, CDER argues that using a pooled analysis in this context is inappropriate and misleading. Different studies followed patients for different lengths of time to collect mortality information, and made different allocations of patients to control arms and treatment arms. When the data are compared using a log-rank test, which is the appropriate test here, they do not demonstrate improvement in OS.[69]

Second, Genentech has also selected some OS data from E2100, and argued that although they do not demonstrate OS benefit, they "suggest that an improvement in survival is more likely than no improvement."[70] Specifically, Genentech notes a difference in the survival curves of patients in E2100 over the first 30 months, and a greater survival rate at the landmark dates of one year and two years.[71] However, a determination about survival benefit must be based upon all of the data, not an analysis of selected time points. Other points could be selected that would give a very different view, even in E2100, which is far the most favorable study for Avastin. For example, at three years, the data show a survival *dis*advantage with Avastin. When we do an appropriate analysis, based on all of the data, E2100 does not show a difference in OS that is statistically significant. And, as noted, other studies, which must also be considered, show less favorable or even negative results.[72] This is not to say that there is a survival disadvantage to

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[68] CDER Hearing Presentation Slide 125. *See also* June 29 Tr. 142-43 (Genentech agrees that it prepared this slide); June 29 Tr. 143:21-144:2 (Dr. Jenkins: So you would agree with the statement that there is no demonstrated overall survival advantage for Avastin in first-line metastatic breast cancer?" Dr. Reimann: Yes.")

[69] CDER Post-Hearing Submission 16.

[70] Genentech Post-Hearing Submission 29.

[71] June 29 Tr. 201:9-14; Genentech Post-Hearing Submission 29.

[72] In the AVADO trial, the difference in median OS favored the control arm (median OS of 30.8 months for the 7.5 mg/kg dose of Avastin plus docetaxel arm vs. 31.9 months for docetaxel control arm, HR 1.103; median OS of 30.2 months for the 15 mg/kg dose of Avastin plus docetaxel arm vs 31.9 months for docetaxel control arm, HR 1.003). Joint Statement, Attachment 2. In RIBBON1, median OS values for the taxane/anthracycline control arm are not

Avastin; the evidence does not demonstrate that. But it does underscore the importance of considering all the data. When that is done, as CDER and Genentech agree, no OS benefit with Avastin has been shown.

2. Avastin has not been shown to be safe for its metastatic breast cancer indication

Because no drug that is active is entirely safe, FDA interprets the concept of safety in relationship to a drug's effectiveness in the intended patient population. In other words, FDA determines whether the drug has been shown to provide a benefit that outweighs its risks. Here, those risks are considerable. As discussed above, CDER and Genentech agree that the safety profile of Avastin is accurately described by its prescribing information. Joint Statement ¶ 22, 23. This information includes a boxed warning, the most serious warning for prescription medication under FDA regulations, and Avastin's labeling warns of toxicities that include gastrointestinal perforations, wound healing complications, and hemorrhage.[73] Avastin's prescribing information also warns that it is associated with more common, serious toxicities, such as hypertension, proteinuria, and increased incidence of chemotherapy-related toxicities such as neutropenia, febrile neutropenia, sensory neuropathy, diarrhea, and hand-foot syndrome. The clinical trials that Genentech has submitted to FDA show that the addition of Avastin to chemotherapy leads to an increase in serious adverse events and grade 3-5 adverse events.[74] In

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available, but the hazard ratio favors the control arm: HR of 1.11 when Avastin plus taxane/anthracycline arm is compared to taxane/anthracycline arm. FDA Briefing Document for 2010 ODAC Meeting, 18, 21.

[73] Joint Statement, attachment 1, at 3. *See also* June 29 Tr. 141:20-142:9 ("Dr. Jenkins: [Y]ou agree that these are serious and potentially life-threatening risks associated with the use of this drug that warrant a boxed warning specifically for Avastin." Dr. Horning: Yes. ... Dr. Jenkins: And did Genentech agree to this boxed warning language, or did FDA order you to implement this language for the safety risk? Dr. Horning: We agreed.").

[74] A "serious adverse event" is an adverse drug experience that:

> (A) results in--(i) death; (ii) an adverse drug experience that places the patient at immediate risk of death from the adverse drug experience as it occurred (not including an adverse drug experience that might have caused death had it occurred in a more severe form); (iii) inpatient hospitalization or prolongation of existing hospitalization; (iv) a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; or (v) a congenital anomaly or birth defect; or (B) based on

the E2100 trial, there was a greater than 20% increase in grade 3-5 toxicities in the Avastin arm compared to the control arm.[75] Additional information is available in a pooled analysis of selected adverse events grade 3 and higher in the first-line trials (E2100, AVADO, and RIBBON1), prepared by Genentech, which shows that there was an increase in all of these adverse events, except for one, in those receiving Avastin plus chemotherapy[76]:

Selected Adverse Reactions	Pooled Chemotherapy (n=982)	Pooled Avastin + Chemotherapy (n=1679)
Any adverse event	23%	37%
Neutropenia	7.1%	10%
Sensory neuropathy	8.5%	9.5%
Hypertension	1.2%	9%
Febrile neutropenia	3.5%	6.5%
Venous thromboembolic event	3.8%	2.8%
Proteinuria	0	2.3%
Arterial thromboembolic event	0.3%	1.6%
Left ventricular systolic dysfunction	1.2%	1.5%
Hemorrhage	0.4%	1.5%
Abnormal Tissue Repair	0.8%	1.7%
Wound dehiscence	0.3%	0.8%
Fistula	0.3%	0.5%
GI perforation	0.3%	0.5%
RPLS	0	<0.1%

None of this is disputed, and because the evidence demonstrates only limited activity of Avastin in tumors, and no clear clinical benefit, the risk-benefit profile of Avastin cannot be considered positive.[77] Indeed, the above data may underestimate risks, because only two of the four studies

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appropriate medical judgment, may jeopardize the patient and may require a medical or surgical intervention to prevent an outcome described under subparagraph (A).

21 U.S.C. § 355-1(b)(4) (this is the definition for "serious adverse drug experience"; "serious adverse event" is a short-hand way of referring to this category of drug experience).

[75] CDER Summary of Arguments 27.

[76] Clinical Review of sBLA 125085\191, at 48 (reproducing Genentech Inc., Integrated Summary of Safety, Appendix B, Table 53, at 202.), available in FDA-2010-N-0621-0145, Appendix 15.

[77] As noted, when ODAC reviewed the data regarding Avastin in July 2010, its members concluded unanimously that the relatively small PFS differentials shown in AVADO did not establish a favorable risk-benefit analysis; 12 of

described here collected information on all adverse events. For example, in the E2100 trial, no data were collected on adverse events that resulted in discontinuation of therapy because of toxicity, and data were not collected that would allow characterization of the duration of toxicity or resolution of toxicity.[78]

Genentech does not dispute the safety information on Avastin's labeling or disavow its pooled analysis, and it acknowledges that the drug comes with serious risks, but it argues that the most common of adverse events, hypertension and proteinuria, are clinically manageable.[79] This does not change the result of the risk-benefit analysis, because substantial benefit has not been shown for Avastin and the risks that remain are serious. Even to the extent that grade 3-5 hypertension and proteinuria can be "managed", they are serious adverse events to which patients should not be subjected without adequate evidence of benefit. Patients are subjected to discomfort, anxiety, and risk of further complications, and are likely to require the administration of additional therapies, in some cases indefinitely. The long-term course of these adverse effects is not fully specified.[80] And, as noted above in the table, hypertension and proteinuria are *not* the only adverse events associated with Avastin. This toxicity profile could be tolerable in a drug

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13 ODAC members concluded that RIBBON1 did not show a favorable result for the combination of Avastin and taxane/anthracylcine or Avastin and capecitabine. Joint Statement ¶ 38.

[78] CDER Summary of Arguments 28.

[79] *See, e.g.*, Genentech Post-Hearing Submission 29-34.

[80] In its submissions and hearing presentation, Genentech has referred to preliminary results from an adjuvant colon cancer study that it agreed to conduct to study the safety profile of Avastin. Genentech argues that results reported for this study indicate that the additional hypertension and proteinuria caused by Avastin's toxicity may be reversible or controllable - for example, by suspending treatment with Avastin or reducing dosage, and by the administration of appropriate therapy. Genentech Post-Hearing Submission 31-32. While this may prove to be useful information for characterizing the long-term safety of Avastin, I note that data for this study have not been submitted to FDA, and the results remain preliminary. In addition, Genentech submitted only a few slides showing topline data five days before the hearing, which limited CDER's opportunity to review even this limited information. Docket No. FDA-2010-N-0621-0354. I also note that even on the most favorable reading for Avastin, the preliminary results indicate that the drug is linked to increases in hypertension and proteinuria at rates consistent with those described on the product's current labeling, and to other adverse events that have not resolved. Genentech Post-Hearing Submission 32.

for which substantial clinical benefit had been demonstrated, but it is not a tolerable set of adverse events in a drug for which clinical benefit has not been shown.

CDER and Genentech disagree about the number of deaths in the first-line trials that should be attributed to Avastin. CDER estimates that the deaths of between 0.8 and 1.7% of the enrolled patients are attributable to Avastin, and notes that Avastin's prescribing information, which Genentech has agreed is accurate, indicates that 1.7% of the patients in the E2100 trial had deaths attributable to Avastin.[81] Genentech argues that CDER has attributed too many deaths to Avastin, and that its drug has been unfairly portrayed as more dangerous than it really is.[82] Without seeking to diminish the importance of these disagreements, I find that for present purposes they are not dispositive. CDER and Genentech agree that Avastin has well established toxicities that increase the number of serious, and even life-threatening, adverse events. And, notwithstanding disagreement about the number of deaths attributable to Avastin, there does not appear to be disagreement that it is responsible for some deaths in the trials, which is further confirmation of its active toxicity.[83] Given this toxicity profile, and the lack of evidence to show substantial benefit, there cannot be a favorable risk-benefit analysis.

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[81] CDER Summary of Arguments 3, 16 (E2100 = 1.7%), 22-23 (AVADO = 0.8%), 24-25 (RIBBON1 = 1.2%). CDER believes this is a conservative estimate, and explains that it only attributed a death to Avastin if the death was caused by a severe toxicity known to be associated with Avastin, and then only after considering the available information in the case history for evidence that another cause could be responsible. *See* CDER Post-Hearing Submission 14-18 (noting, e.g., that "a patient who developed wound healing complications and fistula and died a few weeks later ... was attributed to causes other than Avastin," even though these complications are known to be associated with Avastin; and that "there were examples in which the same [adverse events] occurred in both the chemotherapy-only and Avastin arms of a trial, but ... CDER did not attribute the [adverse events] to Avastin because they could have been caused by chemotherapy.")

[82] Genentech claims that CDER attributed too many deaths to Avastin because it placed too much emphasis on whether a death had been caused by an adverse event known to be related to a toxicity of Avastin, and that CDER did not adequately consider whether there were deaths from similar causes in the chemotherapy-only arms, which would suggest Avastin was not responsible. Genentech Post-Hearing Summary 30-31. Genentech also asserts that the investigators in AVADO and RIBBON1 disagree with CDER regarding attribution of mortality and, although Genentech elsewhere repeatedly agrees that the labeling information for Avastin is accurate, it has raised questions regarding the methodology that produced CDER's mortality estimate for E2100. *Id.* Finally, as noted, Genentech has submitted its analyses of pooled survival data, which conclude that there were fewer deaths in the Avastin arms and equal numbers of treatment related deaths in the Avastin and non-Avastin arms.

[83] As noted, the data do not show an overall survival reduction from Avastin, or a survival benefit.

C. It would not be appropriate to exercise discretion to continue approval for the metastatic breast cancer indication

The final decision I must make is whether to exercise discretion to maintain the approval even though the legal conditions for withdrawal have been met. As noted, FDA may withdraw an accelerated approval when confirmatory trials fail to confirm clinical benefit, or when the evidence does not show that the drug is safe and effective. However, the agency also carefully considers the effect on current and future patients of such a decision, and there may be circumstances, in particular cases, that would lead the agency to conclude that it would be appropriate to exercise discretion and leave an approval in place pending further study. This is not such a case.

Accelerated approval was based on the results of E2100, which showed an effect on PFS that would be large enough to constitute clinical benefit, despite the known risks of Avastin, which are serious. However, we now have five trials[84], and they have substantially changed our view of this drug. The current evidence no longer supports a determination that it has a strong effect in metastatic breast cancer, and it appears likely that its effects are very weak, while the risks associated with this drug remain serious and potentially life-threatening. On this evidence, I cannot find a basis to exercise discretion to continue labeling that would describe this drug as safe and effective for the treatment of metastatic breast cancer. For the population of women with metastatic breast cancer, the evidence does not justify broad exposure to the risks of this drug.

[84] There have been five trials total: three in the first-line setting (E2100, AVADO, RIBBON1), and two in the second-line setting (AVF2119g, RIBBON2). There have, however, effectively been seven independently powered comparison arms, as two of the trials tested more than one chemotherapy partner or a different dose of Avastin.

Genentech has made several arguments about how FDA should proceed that appear to be directed to the exercise of discretion with respect to withdrawal of the accelerated approval[85], and I will address each of those here.

1. Genentech's argument that accelerated approval should be continued as long as there is uncertainty about clinical benefit

Genentech has proposed that FDA leave the metastatic breast cancer approval in place while it conducts additional studies that may confirm the magnitude of effect seen in the E2100 trial. This is in keeping with Genentech's view that approval should be continued for so long as there is uncertainty about whether Avastin may confer clinical benefit[86] -- or, as Genentech sometimes argues in a stronger formulation, that FDA should maintain an accelerated approval until "there is no reasonable likelihood of clinical benefit and no possibility that additional study might further characterize any existing benefit."[87] This is not what FDA or Congress intended in establishing the accelerated approval program, and it is not consistent with the protection of public health. Before FDA may grant accelerated approval, it must make a risk-benefit determination on the basis of evidence provided by the applicant. The labeling that is approved

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[85] Again, I recognize that in some cases these arguments could also be considered to be directed to issues one and two, discussed above. While, for organizational purposes, I discuss them here, they have also been considered in my analysis of the first two issues.

[86] While I reject this Genentech characterization of the standard for continued accelerated approval, I note that, even if I applied the standard that it proposes, the result would be the same. With the number of trials completed, there is not significant uncertainty about the clinical benefit of the use of Avastin with paclitaxel in the treatment of metastatic breast cancer. Genentech's stronger formulation appears simply to be an attempt to describe a standard that would never permit withdrawal of an accelerated approval once granted, as it can never be said that "there is no possibility that additional study might further characterize clinical benefit." In this case, even with the risks associated with Avastin's use, I believe CDER would permit a further clinical study of that use (i.e., CDER would not regard such a study as futile), and I do not see a basis to disagree with that judgment.

[87] "Pre-Hearing Summary of Evidence and Arguments of Genentech, Inc. In Support of Maintaining the Accelerated Approval of AVASTIN® (Bevacizumab) in Combination with Paclitaxel for the First-Line Treatment of HER2-Negative Metastatic Breast Cancer" (Genentech Summary of Arguments) 22, Docket No. FDA-2010-N-0621-0146. *See also* Genentech Post-Hearing Submission 13 ("The accelerated approval statute embodies Congress's intent that the agency accept uncertainty where there is potential benefit and significant unmet need."). It is not entirely clear whether Genentech is arguing that this standard should guide FDA's exercise of discretion, or whether it contends that this is the standard that must be met before FDA may withdraw an accelerated approval. I conclude, for reasons stated in the body of this opinion, that this is not an accurate characterization of the legal standard, and that the grounds for exercising discretion to continue the approval are not met with respect to this indication.

reflects what is known at the time, and it is conditioned on confirmatory studies to verify benefit. When those studies are received, FDA must review them and determine whether, in light of the new information they provide, the risk-benefit determination still favors approval. Where, as here, the studies do not verify the clinical benefit suggested by the initial data and the available evidence does not show the drug to be safe and effective, in the absence of unusual circumstances[88] the accelerated approval should not be continued.

I cannot accept Genentech's proposal that approval be continued until it has time to conduct an additional study of Avastin with paclitaxel that may or may not confirm the PFS gain shown in E2100. Genentech has already conducted additional studies that failed to verify the clinical benefit of Avastin for this use and that failure has altered the risk-benefit calculus for the drug. To grant Genentech's request, I would have to ignore the results of those studies and maintain an approval that is no longer supported by current data, to allow a substantial length of time for more studies on the chance they might confirm benefit. That would be inconsistent with the statute and protection of public health.[89]

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[88] The fact that the statute and regulations give FDA discretion on withdrawal demonstrate that there may be some circumstances in which FDA can decide to continue accelerated approval, while additional investigations are completed, despite disappointing results in the confirmatory studies. It is for this reason that I have carefully considered the various arguments that Genentech has made on this point.

[89] It is worth noting that continuing the metastatic breast cancer indication pending completion of an additional study would mean that the drug would remain approved for years. While there is necessarily some uncertainty about the time that would be needed to conduct Genentech's proposed study, even the most favorable projections indicate that a substantial analysis of the results would not be available for three to four years, and the study could take longer or be infeasible. Genentech believes it could begin enrolling patients in the first quarter of 2012, and that final PFS data would become available in mid-to-late 2016, with the analysis to take additional time. Genentech believes it will be possible to construct an interim "futility analysis" that would trigger early withdrawal if some threshold is not met, "to occur" late in 2015 or in mid-2016. Genentech Post-Hearing Submission 42. However, complications are certainly possible, and planning for this study was not complete at the time of the hearing. For example, if the indication were continued, it is possible that Genentech would have difficulty enrolling patients in a trial in which some would receive paclitaxel plus Avastin (an approved drug for the indication to be tested) while others would receive paclitaxel plus a placebo. Genentech believes this problem would not significantly delay enrollment, but at this point there is uncertainty. At the hearing, Genentech indicated that it had not yet completed a feasibility assessment, and it has not proposed criteria for its interim analysis, or indicated what it believes should occur if it continues to disagree with CDER about what constitutes clinical benefit for this drug in the metastatic breast cancer context. June 29 Tr. 66:18-22.

Withdrawal here is the essential counterpart to accelerated approval. When the accelerated approval pathway was established, it was done with full recognition of the risk that drugs might be approved and later found not to confer clinical benefit to patients. FDA deemed this a risk worth taking for life-threatening illnesses in need of additional therapies, but also found it essential to mitigate that risk by providing for follow-up studies and withdrawal when benefit is not confirmed. The program has, on the whole, worked very well, making many new drugs available, particularly to cancer patients and AIDS patients, years before they would otherwise have been on the market. But when follow-up studies fail to confirm benefit, it is essential that approval be withdrawn in order to protect patients.[90]

2. Genentech's argument that accelerated approval should be continued on the basis of labeling changes and marketing restrictions

Genentech has proposed that the approval could be continued with changes in the marketing and labeling of the drug that would, in its view, focus the metastatic breast cancer indication and marketing on patients who "have the greatest unmet medical need, and present the most favorable benefit-risk profile."[91] In particular, Genentech proposes to modify Avastin's labeling to inform prescribers that it is indicated for use in patients who have "disease characteristics (e.g., aggressive HR+/HER2- or HR-/HER2- tumors) for which other therapies are considered to be less appropriate per physician assessment."[92] Genentech also proposes to implement a companion Risk Evaluation and Mitigation Strategy (REMS) "focused on an enhanced communication plan and a patient Medication Guide" that would provide additional information,

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[90] 57 Fed. Reg. at 13238.

[91] Genentech Post-Hearing Submission 37-38.

[92] Genentech Post-Hearing Submission, Appendix A, Proposed Labeling at 5. "HR" as used by Genentech refers to hormone receptor (estrogen receptor (ER) or progesterone receptor (PR)). *See id.*, Appendix C: "Discussion Paper: HER2-Negative Metastatic Breast Cancer – A Clinically Heterogeneous Disease" at 2. Tumors may be either positive or negative for hormone receptors and either positive or negative for HER2 (human epidermal growth factor receptor).

and submit promotional pieces to FDA before use. It is also "open to discussing limitations on its marketing on Avastin."[93]

The problem with this proposal is that it would create labeling and a marketing plan that are not supported by the data. The data do not demonstrate that Avastin plus paclitaxel is effective for patients with HR+/HER2- or HR-/HER2- tumors, or that the risks associated with its use are reduced in such patients. There are no data to demonstrate that they enjoyed greater PFS benefits or any OS benefit than the trial population as a whole, or that adding Avastin to the chemotherapy treatment of this group would improve their quality of life.[94] With respect to patients with triple-negative breast cancer[95] in particular, a group to which Genentech's expert gave special attention, CDER conducted an exploratory analysis of the first-line trials Genentech has submitted, segregating the triple-negative patients from other patients, and found that the overall survival and progression-free survival results of the triple-negative breast cancer patients are similar to the results for other patients.[96] Nor has Genentech identified another group of patients for whom other therapies would be "considered to be less appropriate" than Avastin.[97]

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[93] Genentech Post-Hearing Submission 38.

[94] *See* June 29 Tr. 257:19-259:8; Office Director Memo Supporting the NOOH 5 ("While it is possible that some patients may receive clinical benefit from Avastin for treatment of breast cancer, the available data are not sufficient to demonstrate that such a subgroup exists and, if so, how to identify the patients in advance."), Docket No. FDA-2010-N-0621-0145, Appendix 21. Genentech included an analysis in its posthearing submission that purports to show a benefit for patients characterized as triple negative. Genentech Post-Hearing Submission, Appendix C, "Discussion Paper: HER2-Negative Metastatic Breast Cancer – A Clinically Heterogeneous Disease." That analysis is not convincing. First, it is an exploratory analysis. As such, it may support a hypothesis for future testing, but is not itself compelling evidence. Moreover, the reported hazard ratio for PFS for this subgroup is not very different from the ratio for the study as a whole, and the confidence interval for the claimed benefit with respect to overall survival in this subgroup includes the possibility that the use of Avastin decreases rather than increases survival.

[95] Genentech refers to tumors that are ER-/PR-/HER2- as "triple negative." *See* Genentech Post-Hearing Submission, Appendix C, at 2.

[96] June 29 Tr. 258:6-258:20; CDER "Referenced Slides" 10-11, Docket No. FDA-2010-N-0621-0360.

[97] I do note that Genentech's clinical expert and some members of the public argued that increases in PFS represent a benefit because it relieves symptoms associated with tumor growth, and that this benefit is especially important for patients who are heavily tumor-burdened. As noted, however, the data as a whole do not demonstrate a substantial increase in PFS. And, the studies that surveyed patients about their experience on the drug did not show an improvement in quality of life; this was true even among women who showed objective response – a measured reduction in tumor size after therapy. June 29 Tr. 232:7-9, 233:2-4. Although it would be useful to be able to

Accordingly, FDA cannot approve labeling that would inform patients and prescribers it believes the drug is safe and effective, or incorporate the standard for "physician assessment" into the labeling. For the same reasons, the proposed REMS plan is also inappropriate. A REMS plan may be approved where FDA determines that communication regarding the drug is "necessary to ensure that the benefits of the drug outweigh the risks of the drug." 21 U.S.C. § 355-1(a)(2)(A). Here, there is no basis to conclude that the proposed communication would lead to clinical benefit that would outweigh Avastin's risks.

Genentech also argues that approval for the metastatic breast cancer indication should be maintained for patients who are triple-negative or HER2- because Avastin offers a therapeutic improvement over the combination therapies that are often indicated for these patients, and particularly when compared to the most commonly prescribed chemotherapy combinations, which offer results "much more in line with AVADO and RIBBON1 than E2100."[98] This argument repeats and depends on Genentech's view that the benefit of Avastin plus paclitaxel is characterized by E2100, a conclusion that is not viable in light of the four other trials from which data have been submitted. As a whole, the evidence available does not demonstrate that Avastin plus paclitaxel would confer meaningful clinical benefit in light of its serious risks.[99] Thus, I do

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directly compare women who were heavily burdened with symptoms at the start of the trials to other women, this cannot be done because no data were collected on patient symptoms at enrollment. From the little information that is available, it appears likely that most women in the trials (which were first-line trials) were asymptomatic or had mild symptoms at the time they enrolled. June 28 Tr. 170:11-17; June 29 Tr. 257:19-258:5.

[98] Genentech Post-Hearing Submission 26.

[99] Genentech submitted a "discussion paper" regarding the safety and efficacy profile of alternatives to Avastin in the appendix to its Post-Hearing Submission on August 4, 2011. CDER has not had an opportunity to respond to this paper, and it is questionable whether it was appropriate for Genentech to file this in a post-hearing submission that was to discuss its views of what took place in the hearing. Nevertheless, I have considered this paper in making my decision.

not find this modification to be a basis to exercise my discretion to continue the accelerated approval.[100]

3. Genentech's argument that approval should be continued while studies are completed to determine whether a subset of patients who would benefit from the drug may be identified

If it were possible to identify patients who would have a favorable response to Avastin before they begin taking the drug, we might be able to improve the risk-benefit profile of the drug by limiting the indication to those women. Genentech has proposed two hypotheses, but at this point the data do not support either.

First, Genentech has suggested that patients with high plasma levels of certain kinds of Vascular Endothelial Growth Factor (VEGF), particularly VEGF-A, "may be more likely" to benefit from Avastin.[101] There is very little evidence to support this hypothesis. Studies have not been conducted to test it, and the evidence that is currently available is, at best, mixed. In support of the hypothesis, Genentech notes that in an exploratory analysis of a subset of patients in the AVADO study, it found a favorable PFS hazard-ratio at certain VEGF-A levels, suggesting that those with high levels of VEGF-A may be more likely to derive substantial benefit from Avastin.[102] However, this kind of exploratory analysis is not able to provide a valid estimate of the magnitude of benefit. Moreover, as CDER points out and Genentech does not dispute, in the E2100 trial "there was no correlation between tumor tissue VEGF expression levels and outcomes in the subset of patients for whom tissue samples were available," and in a retrospective analysis of the AVF2119g trial, there was "no observed predictive effect of VEGF-

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[100] Technically, Genentech is not proposing here to maintain approval for the indication, but rather to modify it. If I had found that its proposal had merit, this would raise some difficult procedural questions about how the modifications would be made. Because I do not find merit in the proposal, I do not address them.

[101] Genentech Request for Hearing 63. *See also* Genentech Post-Hearing Submission 42 ("[P]lasma VEGF-A *may* be a *potential* predictive marker for Avastin activity.") (emphasis added).

[102] Genentech Post-Hearing Submission 42.

A."[103] The reason Genentech has designed a study to test its hypothesis about VEGF-A is that it is simply not known whether women with higher plasma levels of VEGF-A respond better to Avastin.

Second, as noted above, Genentech has not shown that the Avastin-paclitaxel combination is appropriate for patients who are burdened with greater or more aggressive tumors, such as patients who are triple-negative or HER2 double-negative. In sum, the data do not currently identify a group of patients for whom clinical benefit is confirmed, and continuing accelerated approval while waiting for evidence is not appropriate. Genentech may, of course, continue to pursue its hypotheses by new investigations of Avastin under an investigational new drug application and FDA will carefully review the results of any such studies that are submitted.

4. Genentech's argument that FDA has maintained approval for Gemzar, and has exercised discretion to maintain approval for other drugs

Genentech argues that the Avastin efficacy data compare favorably to data that support the approval of Gemzar, another first-line treatment for metastatic breast cancer, and that Gemzar's safety profile is not substantially better than that of Avastin.[104] As noted, prior to the hearing, Dr. Midthun explained that the hearing would not extend to CDER's decisions with respect to other products for the treatment of metastatic breast cancer, or of other products approved under the accelerated approval program. Each decision to withdraw or not to withdraw the approval of a product must be made on its own merits. If the decision with respect to another product is in error, that would not justify continuing that error with respect to the metastatic breast cancer indication for Avastin. *See Edison Pharm. Co., Inc. v. Food and Drug Admin.*, 600 F.2d 831, 843 (D.C. Cir. 1979). Moreover, as a practical matter, it is not possible to evaluate the

[103] CDER Post-Hearing Submission 24 n.105.
[104] Genentech Post-Hearing Submission 2.

different circumstances associated with decisions with respect to other products in the context of this or any proceeding.[105]

Genentech argues that FDA has exercised discretion to allow time for additional studies on other occasions where the facts were significantly less compelling. In particular, it cites the examples of erbitux, midodrine[106], and doxorubicin. Again, it is simply not appropriate (and as a practical matter is not possible) for a hearing of this type to explore the multiple factors that go into decisions with respect to other products and to weigh those decisions against the one being considered in the hearing.

5. Genentech's argument that accelerated approval should be continued because CDER did not clearly communicate, or changed its mind with respect to, what was required for confirmation of clinical benefit

Genentech argues that CDER changed the standard for converting accelerated approval into regular approval midstream, and that it would have designed a different study if it had realized that the results shown in AVADO and RIBBON1 would not support approval.[107] Genentech notes that CDER had preliminary PFS data from the AVADO study when it gave accelerated approval, though those data showed an increase in median PFS of only 0.8 months. Genentech also notes that when it met with CDER in February 2009, CDER had top-line data for both AVADO and RIBBON1 (which showed increases in median PFS of 1.2 and 2.9 months), and that the minutes for that meeting state that conversion of the Avastin plus paclitaxel approval to

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[105] At the time that Gemzar was approved, the available data suggested a trend in favor of extended overall survival. Ultimately, that survival benefit was not proven. Genentech, of course, is not arguing that the approval for Gemzar should be withdrawn, but rather that the PFS values from the Gemzar study should be compared to those for Avastin, despite the lack of any such survival trend for Avastin.

[106] CDER announced its decision to withdraw the accelerated approval of midodrine, and the applicant has requested a hearing on that decision. *See* Notice of Opportunity for Hearing, August 16, 2010, Docket No. FDA-2007-N-0475-0019; Genentech Request for Hearing, September 16, 2010, FDA-2007-N-0475-0026.

[107] *See, e.g.*, Genentech Post-Hearing Submission 6-7.

regular approval would follow from "demonstrated improvement in progression-free survival and evidence that survival is not impaired."[108]

Whether Genentech might have proposed a different trial to confirm benefit is not, of course, relevant to the evaluation of Avastin FDA must make today. Whatever a future trial may show, adequate and well-controlled confirmatory trials have already been conducted and data submitted, providing information about the drug that there is no public health basis to ignore. Certainly, hypothetical future results do not provide a reason to look past the data that is now before the agency.[109]

With respect to the regulatory standard, CDER points out that it informed Genentech on a number of occasions that regular approval for Avastin would depend on the magnitude of PFS improvement it could demonstrate. CDER communicated this during teleconferences in 2004[110] and 2006,[111] and in 2007 it adopted the PFS policy under which the agency intended to evaluate the magnitude of PFS differential in deciding whether it constituted clinical benefit. At the 2007

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[108] *Id.* at 7.

[109] With respect to the question of whether there may have been unfairness to Genentech, I note that Genentech designed and began the AVADO and RIBBON1 trials well before accelerated approval was given for the metastatic breast cancer indication, with the apparent goal of obtaining approval not only for the chemotherapy partners used in those trials, but also for a broader, taxane-based indication. These studies were not designed or powered to respond to the February 2009 meeting that Genentech cites, and were submitted to regulatory agencies for other countries, not just FDA.

[110] The minutes of an October 28, 2004 teleconference between Genentech and CDER to discuss study planning for the E2100 trial indicate that "Genentech asked if PFS is an adequate endpoint for full approval," and CDER replied "that it depends on the overall dataset and magnitude of PFS." October 28, 2004 Teleconference Minutes, at 3, Docket No. FDA-2010-N-0621-0145, Appendix 22. Genentech also agreed to provide survival data at the time of the PFS analysis. *Id*

[111] During a January 10, 2006 teleconference, CDER stated that "progression free survival and preliminary overall survival data from study E2100 would potentially support an accelerated approval for the use of Avastin in combination with paclitaxel for chemotherapy naïve patients with locally recurrent or metastatic breast cancer. Mature data concerning overall survival will be requested as a post-marketing commitment and would serve to convert the sBLA from accelerated approval to regular approval." Type B Meeting Minutes (January 10, 2006), Docket No. FDA-2010-N-0621-0145, Appendix 24. When Genentech "expressed concern about waiting for the survival data to convert to regular approval from accelerated approval," FDA stated that "the data needed to be mature. Progression-free survival has been discussed as an end point supporting regular approval for metastatic breast cancer: FDA will consider whether the data provided will support regular approval during the course of the review. *It depends on the strength of the data and the effect size whether approval is accelerated or regular*." *Id.* (Emphasis added.)

ODAC meeting at which Avastin's supplemental application for the metastatic breast cancer indication was discussed, representatives of CDER clearly stated that the size of the PFS differential was of central importance, and often discussed that size in terms of the 5.5-month increase in median PFS shown in E2100, a fact that Genentech appears to concede.[112] When Avastin received accelerated approval, rather than regular approval, the Director's memorandum and attached reviews noted CDER's continuing questions about the magnitude of Avastin's effect on PFS.[113] With respect to CDER's review of preliminary information from other trials, the agency did not indicate that its review constituted agreement that the trials had confirmed clinical benefit, and Genentech does not appear to have relied only on the PFS data; for example,

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[112] The briefing document that CDER prepared for the meeting stated: "The key issue of this sBLA for ODAC consideration is whether an estimated 5.5 month improvement in median PFS, with no statistically significant improvement in survival is adequate to support approval of bevacizumab with paclitaxel for first line treatment of patients with metastatic breast cancer." FDA Briefing Document for 2007 ODAC Meeting, 27. The transcript for this meeting contains many statements regarding the importance of demonstrating magnitude of benefit, and both CDER and Genentech discussed that question with reference to the number of months that median PFS had increased. *See, e.g.*, 2007 ODAC Meeting Tr. 15:12-16 (Dr. Pazdur: "Important considerations on the use of PFS as an endpoint should include *the magnitude of effect on PFS*, the treatment's toxicity profile, and the clinical benefits and toxicities of available therapy.") (emphasis added); *Id.* at 122:16-123:3 (Dr. Pai-Scherf (CDER): "[T]his application rests solely on evidence of an improvement on PFS in a single study. A 5.5 months improvement in PFS is claimed by Genentech. In considering Genentech's claim, the *FDA* needs to verify the robustness. That is, is there an effect? *And if there is an effect, the magnitude. That is, is the 5.5-month improvement in PFS reliable*?") (emphasis added) *Id.* at 89:5-8, 16-21 (Dr. Winer (Genentech)"[F]or progression-free survival to equal benefit, for it to be meaningful, this progression-free survival needs to be *substantial in magnitude*.... In terms of the magnitude of the benefit, *as you've heard now multiple times*, the improvement in outcome in terms of progression-free survival is substantial with a hazard ratio of. 48 *and an absolute improvement of 5-1/2 months*.") (emphasis added). *See also* June 29 Tr. 119:14-16 (Mr. Labson: "The issue isn't whether CDER said that magnitude would be considered, which I think is pretty straightforward.")

[113] *See* Dr. Richard Pazdur, Office Director's Memo re Re: STN 125085/91 (Feb. 21, 2008) , 5 ("The FDA clinical and statistical reviews and ODAC presentations state that Avastin's effect on the PFS endpoint is robust, but question the effect's magnitude."). These concerns were of sufficient importance to the Division Director, Dr. Patricia Keegan, that she recommended a complete response (i.e., no approval or accelerated approval) until the magnitude of benefit could be confirmed. Division Director Decisional Review (Feb. 21, 2008), 1-2 ("Major issues arising during this application were evidence of a treatment effect in only one of two trials and uncertainty regarding the magnitude of the effect on progression-free survival in the single positive trial. ... [T]he recommendation [of a complete response] is based on the applicant's failure to characterize the magnitude of the treatment effect, which is necessary for the determination of the relative benefits given the known risks of Avastin.") Both memoranda available in Docket No. FDA-2010-N-0621-0145, Appendix 11.

in the AVADO trial, it called out what appeared to be positive trend for Avastin with regard to OS.[114]

On balance, I believe that Genentech understood, or should have understood, that approval would turn on the magnitude of PFS gain shown. Ultimately, of course, even if I were to decide that there was a miscommunication with Genentech, that would not change my decision with respect to the approval. I must make my decision on the basis of whether the drug has been shown to provide a measurable overall benefit that would justify its use in light of its risks for the patients who might use it, based on the studies that are available.

Genentech does raise one significant issue, discussed above, about the magnitude of increase in median PFS it would have to achieve in order to convert accelerated approval for this indication to regular approval. While it seems clear that the result demonstrated by AVADO does not constitute clinical benefit,[115] and CDER has indicated that the results shown in E2100 do constitute clinical benefit, the threshold at which a trial would pass from failure to success has been difficult to draw ahead of time with great precision. Unfortunately, this problem is not easy to overcome. The agency has had limited experience using PFS as a measure of clinical benefit in the context of first-line therapy for metastatic breast cancer, and the analyses of safety and

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[114] CDER Hearing Presentation Slide 95. As noted, when the data and final analyses for AVADO were finally presented, Genentech agrees that no OS benefit was established. Genentech does not represent that CDER stated that the preliminary results of AVADO or RIBBON1 would constitute clinical benefit if confirmed in a mature submission. At the February 2009 meeting that Genentech alludes to, Genentech specifically asked whether FDA agreed that the data from AVADO and RIBBON1 "[s]upport full approval of Avastin for the treatment of patients who have not received chemotherapy for metastatic, HER2-negative breast cancer?" FDA responded: "The adequacy of the data to support expanded labeling claims will be determined upon review of the data." Type B pre-sBLA Meeting Minutes (February 26, 2009), 4, Docket No. FDA-2010-N-0621-0145, Appendix 24. When Genentech asked whether the studies had satisfied its postmarketing commitment under the accelerated approval regulations, FDA responded that "[t]he adequacy of the data to fulfill the [postmarketing commitment] can only be determined upon review of the supplement." *Id.*

[115] Median PFS gain 0.8 or 0.9 months, HR 0.62 or 0.70. Even Genentech does not argue strenuously that this study showed clinical benefit, and it has said that it respects the decision by EMA not to approve an indication for the Avastin-docetaxel combination. June 29 Tr. 129:12-17 (Dr. Horning: "[W]e do recognize that the tolerability of docetaxel in combination with Avastin is less good than with paclitaxel, and we respect the judgment of those who've used the two in combination as well as the decision that was made in Europe.")

efficacy data required to make an approval decision for a drug such as Avastin are exceedingly complicated. With respect to Avastin, CDER has now informed Genentech that demonstrating an improvement in PFS like that shown in E2100 will support conversion to regular approval, assuming there are no new safety signals to change the risk-benefit calculus and no evidence of decreased overall survival. Pending such a demonstration, or a showing of some other clinical benefit that could support approval, I conclude that the approval must be withdrawn.

6. The suggestion that accelerated approval should be continued because of the views of other regulators and expert organizations

Genentech notes that other regulators and some scientific bodies have reached a different conclusion than CDER with respect to Avastin. I will discuss these in turn, but first want to note a common theme. FDA respects and is interested in the views of other regulators and the medical community, but it must ultimately make an independent scientific judgment about the risk-benefit analysis of Avastin, adhering to controlling legal authority and on the basis of the data before us. Other regulators and medical bodies operate under their own laws or objectives, and in some cases scientists and clinicians will simply reach different conclusions about the very difficult medical questions that the evaluation of drug products may present. I also note that some experts not cited by Genentech do not find this drug safe and effective for metastatic breast cancer. In light of the nature of the disagreements Genentech has cited, I see no basis to question the conclusions announced here.

With respect to regulators, Genentech observes that other countries have approved Avastin plus paclitaxel for first-line treatment of metastatic breast cancer, and that in particular the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use

(CHMP) has done so.[116] CDER has reached different scientific conclusions than the EMA before, including with respect to Avastin. For example, CDER has granted accelerated approval for the use of Avastin for the treatment of glioblastoma multiforme, while the EMA has not approved this use.[117] With respect to the metastatic breast cancer indication, I also note that there are important areas of agreement. For example, CDER and the EMA agree that the studies submitted by Genentech show no benefit to OS or quality of life, and that the docetaxel-Avastin combination should not be approved because it showed very modest benefit in the AVADO trial.[118] The principal difference between the agencies relates to the Avastin-paclitaxel combination, with respect to which the EMA granted full approval in February 2007, before the data from AVADO and RIBBON1 were available, and before independent analysis to resolve significant methodological issues cited by CDER. *Id.* This does not suggest a basis for questioning CDER's decision.

Genentech also notes that the National Comprehensive Cancer Network (NCCN) recommended the use of Avastin plus paclitaxel in its 2010 Clinical Practice Guidelines for

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[116] Genentech Post-Hearing Submission 15-16. I also note that another important national regulatory agency, the Pharmaceutical and Medical Device Agency in Japan, has granted approval to Avastin for a somewhat different breast cancer indication. Genentech has informed FDA that that agency has recently approved the use of Avastin in combination with paclitaxel for inoperable or recurrent breast cancer, apparently without restriction to first-line therapy or to use in HER2 negative breast cancer. September 27, 2011 email communication from Genentech counsel Michael Labson to Dr. Midthun, Docket No. FDA-2010-N-0621-0535.

With respect to another U.S. Government agency, Genentech also states that, after the June hearing, the U.S. Department of Health and Human Services Center for Medicare and Medicaid Services (CMS) indicated that "for the present time Medicare would continue to cover Avastin for metastatic breast cancer." Genentech Post-Hearing Submission 44. CMS did not indicate any opinion regarding the risk-benefit analysis of the Avastin-paclitaxel combination under the FD&C Act, and operates under different legal requirements than FDA. In particular, it may decide to pay for off-label uses of approved drugs when these are prescribed by physicians. By contrast, the United Kingdom's National Institute for Health and Clinical Excellence (NICE) has not supported Avastin for breast cancer. It concluded that: "The evidence for the effectiveness of bevacizumab in prolonging survival was not robust and overall did not show enough of a demonstrable benefit for it to be considered a cost-effective use of NHS resources."
http://www.nice.org.uk/newsroom/pressreleases/AvastinBevacizumabNotRecommended.jsp. *See also* http://guidance.nice.org.uk/TA214.

[117] CDER Summary of Arguments 45.

[118] CDER Summary of Arguments 47.

Breast Cancer, and that after the June hearing it reaffirmed these guidelines.[119] While CDER, and I, respect the scientific and clinical expertise of the NCCN panels, ultimately FDA must make its decision on the basis of the evidence. I note that CDER has received advice from medical experts on the ODAC, who have extensive qualifications in clinical trial design and evaluation, and are in a better position to review and make decisions relating to this approval.[120] They have been provided with detailed information regarding the trials and data submitted to support the indication, including presentations from CDER and Genentech regarding the completeness, accuracy, and quality of the data. They are then able to make recommendations on the basis of high-level evidence, and on that basis concluded, on two occasions, that the approval should be withdrawn. The NCCN panel has a different objective in publishing its recommendation, which is to provide clinicians with ready access to synthesized information they can use in making patient decisions. NCCN's Avastin recommendation, like many NCCN recommendations, was based on "lower level evidence" which "may include non-randomized trials; case series; or when other data are lacking, the clinical experience of expert physicians."[121] I also note that, in keeping with ODAC's regulatory purpose, its members are carefully screened for covered relationships, and are not permitted to serve if these present even an appearance of a conflict that could affect their impartiality.[122] NCCN receives financial support from Genentech

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[119] Genentech Summary of Arguments 25-26; Genentech Post-Hearing Submission 43-44.
[120] The July 2010 panel included four voting members who have authored a number of peer-reviewed publications on breast-cancer treatment (Drs. Freedman, Grem, Loehrer, and Wilson), and two temporary voting members, Drs. Budzar and Mortimer, were appointed to serve because of their breast cancer experience. CDER Summary of Arguments 49, 50.
[121] *See* Genentech Post-Hearing Submission 15 (indicating that the recommendation was level 2A); *NCCN Guidelines™ and Derivative Information Products: User Guide*, available at http://www.nccn.org/professionals/transparency.asp (accessed August 12, 2011) (explaining that category 2A represents "lower-level evidence" and the meaning of that term).
[122] 5 C.F.R. § 2635.502.

to distribute independently developed content, and one-third of the members of the NCCN Breast Cancer Panel have received financial support from Genentech.[123]

7. The suggestion that ODAC members' recommendations should not be given "undue weight"

Finally, in its Post-Hearing Submission, Genentech argues that I should not give "undue weight" to the votes of the ODAC panel, arguing that the members' votes reflected pre-existing views, that the panel lacked clinical experience with breast cancer and Avastin, and that ODAC took the position that PFS gain cannot support a drug approval.[124] As I have noted throughout, the decision with respect to this approval is mine alone. While I considered the advice of the advisory committee, I did so in light of the evidence in the record, including presentations of the parties' representatives, Genentech's experts, and public comments. In addition, Genentech has not pointed to substantial evidence in support of its specific criticisms of the ODAC, and has given no reason to doubt that they attended carefully to the proceedings, clearly understood the issues presented, and gave their advice on the basis of the evidence.[125] I also note that when the hearing in this matter was granted, Dr. Midthun informed Genentech by letter that if it believed additional expertise would be helpful it would have the opportunity to present experts of its

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[123] CDER Summary of Arguments 51.

[124] Genentech Post-Hearing Submission at 44-48.

[125] With respect to the ODAC members' clinical knowledge, Genentech does not identify any clinical or practical information that, properly understood, would have led to a different recommendation, or show that ODAC members' recommendations were premised on misunderstanding of clinical information. For example, Genentech emphasizes testimony from its breast-cancer expert that there are ways to manage hypertension and proteinuria, but it gives no reason to doubt that ODAC members understood the evidence presented on this subject, and as noted above in section V.B.2., notwithstanding this evidence Avastin plainly has risks that outweigh its benefits. At bottom, Genentech's disagreement appears to be with the way ODAC experts weighed the evidence, rather than their ability to do so.

Genentech's argument that ODAC members prejudged the subject of this hearing depends mostly on the fact that some of them previously provided recommendations to CDER regarding Avastin and made public statements about those recommendations. Genentech Post-Hearing Submission 44 n.120. These statements were, however, not of a nature that would require disqualification. FDA regulations do not require ODAC members to refrain from voting more than once on a question relating to a drug or drug approval, and in fact this happens fairly often. For example, members of ODAC who voted in favor of Avastin in 2007 were not barred from voting when Genentech's sBLAs in which it sought regular approval for Avastin were discussed in 2010.

choosing.[126] Genentech availed itself of that opportunity, and I have taken its experts' views into account. Genentech's view that the ODAC rejected PFS as a basis for approval is also seriously overstated.[127] In any event, my decision in this case is based upon Genentech's failure to confirm a substantial PFS gain for Avastin, and the drug's risk profile; it is not a rejection of PFS as a basis for approval in cases where PFS gains that are substantial in light of the risks of the drug can be shown.

VI. CONCLUSION

For all of the reasons explained above, I am withdrawing the accelerated approval of Avastin for use with paclitaxel in the treatment of metastatic breast cancer. I appreciate the significant effort that Genentech has put into developing this drug for this disease, as well as for other cancers, and the excellent presentation it made in the hearing. I trust that it will continue its investigations into use of the drug in those circumstances that it believes to be promising, and if new data are submitted they will be considered. Ultimately, however, I conclude that the

[126] February 23, 2011 letter from Dr. Midthun to counsel for Genentech and CDER, Docket No. FDA 2010-N-0621-067. This letter also informed Genentech that FDA regulations required the participation of an advisory committee at the hearing, and that the agency interprets its regulations to require that the advisory committee in this proceeding be the ODAC. Genentech did not object to this determination. The number of members seated at the hearing was a function of the number serving on the ODAC at the time of the hearing, and screening required by statutes and regulations to ensure that only members without conflicts would be seated.

[127] Genentech identifies three statements in support of its view that the ODAC rejected PFS as a possible basis for approval. Two of these statements were made by Dr. Logan and Dr. Compagni-Portis, who were stating only that it may be difficult to identify the level of PFS that constitutes clinical benefit, and did not say they opposed it as a basis for approval. Both identified Genentech's failure to confirm a substantial PFS benefit in explaining their votes. *See, e.g.*, June 29 Tr. 214:1-11, 224:22 – 225:7. A third panelist, Dr. Sekeres, also noted the failure to confirm benefit, but also that Genentech had failed to demonstrate an improvement in quality or duration of life, and this may have been part of his understanding of what was required to continue the approval. *See* June 29 Tr. 219:21-220:18; 229:16-22. I have considered Dr. Sekeres' recommendation, note Genentech's objections, and make my decision for the reasons given in the body of this opinion.

currently available data do not support continued accelerated approval of this drug for this indication.

Dated: November 18, 2011

Margaret A. Hamburg, M.D.
Commissioner of Food and Drugs